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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
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Thiazole derivatives and use thereof

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Thiazole derivatives and use thereof

Field of the invention

This present invention is related to the use of thiazole derivatives of Formula (I) for the treatment and/or prophylaxis of autoimmune disorders and/or inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, allergy, asthma, pancreatitis, multi-organe failure, kidney diseases, platelet aggregation, cancer, sperm motility, graft rejection or lung injuries. Specifically, the present invention is related to thiazole derivatives for the modulation, notably the inhibition of the activity or function of the phosphoinositide-3-kinases, PI3Ks.

Background of the invention

Phosphoinositide 3-kinases (PI3Ks) have a critical signalling role in cell proliferation, cell survival, vascularization, membrane trafficking, glucose transport, neurite outgrowth, membrane ruffling, superoxide production, actin reorganization and chemotaxis (*Cantley, 2000, Science , 296, 1655-1657 and Vanhaesebroeck et al., 2001, Annu. Rev. Biochem., 70, 535-602).*

The term PI3K is given to a family of lipid kinases which, in mammals, consists in eight identified PI3Ks that are divided into three sub-families according to their structure and their substrate specificity.

Class I group of PI3Ks consists in two sub-groups, Class IA and Class IB.

Class IA consists in a 85 kDa regulatory unit (responsible for protein-protein interactions via the interaction of Src homology 2 (SH2) domain with phosphotyrosine residues of other proteins) and a catalytic sub-unit of 110kDa. Three catalytic forms (p100α, p110β and p110δ) and five regulatory isoforms (p85α, p85β, p55γ, p55α and p50α) exist for this class.

Class IB are stimulated by G protein βγ sub-units of heterodimeric G proteins. The only characterized member of Class IB is PI3Kγ (p110γ catalytic sub-unit complexed with a 101-kDa regulatory protein, p101).

Class II PI3Ks comprises α, β and γ isoforms, which are approximately of 170 kDa and characterized by the presence of a C-terminal C2 domain.

Class III PI3Ks includes the phosphatidylinositol specific 3-kinases.

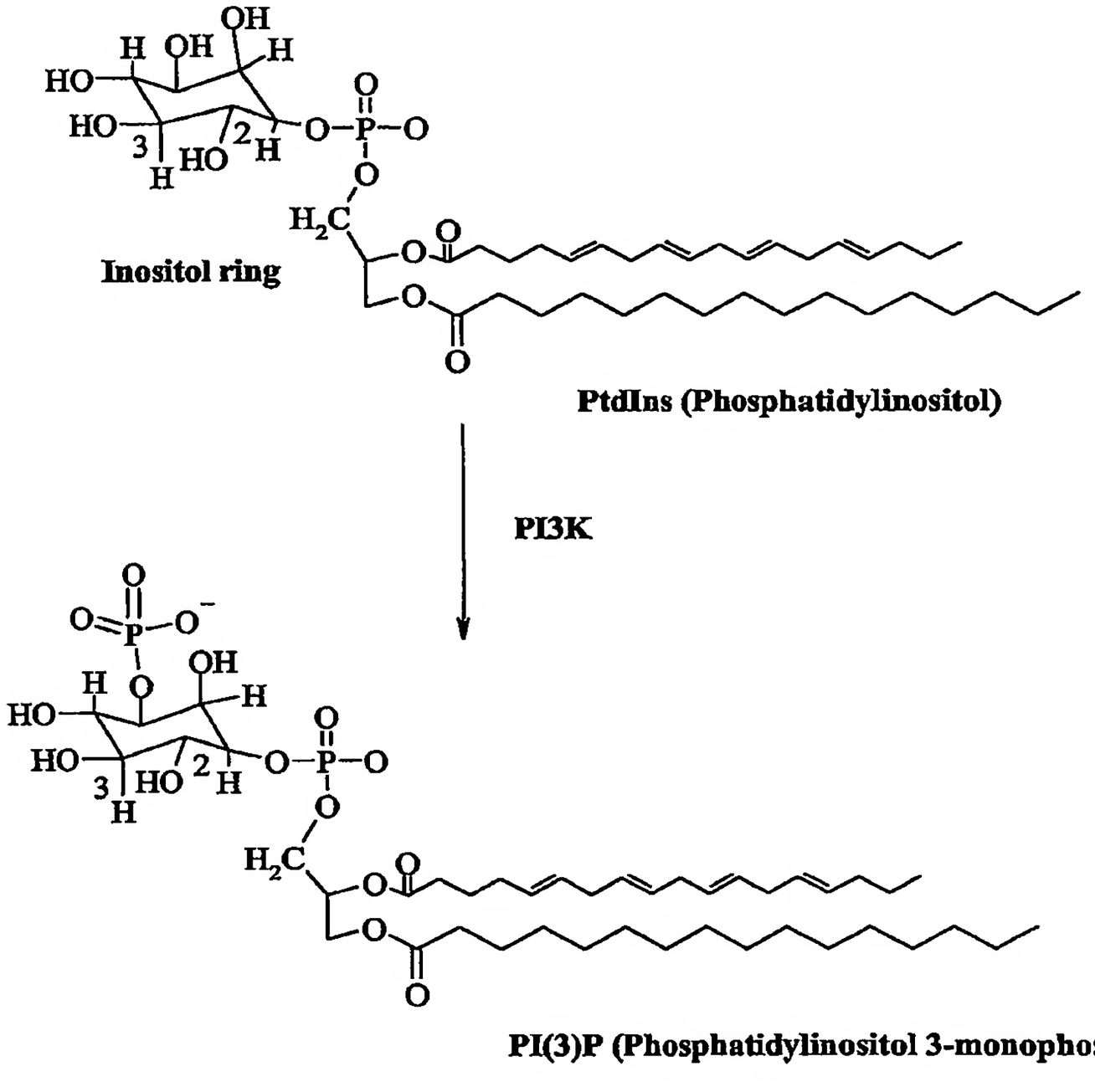
The evolutionary conserved isoforms p110α and β are ubiquitiously expressed, while δ and γ are more specifically expressed in the haematopoetic cell system, smooth muscle cells, myocytes and endothelial cells (*Vanhaesebroeck et al., 1997, Trends Biochem Sci., 22(7), 267-72*). Their expression might also be regulated in an inducible manner depending on the cellular-, tissue type and stimuli as well as disease context.

PI3Ks are enzymes involved in phospholipid signalling and are activated in response to a variety of extra-cellular signals such as growth factors, mitogens, integrins (cell-cell interactions) hormones, cytokines, viruses and neurotransmitters and also by intra-cellular cross regulation by other signaling molecules (cross-talk, where the original signal can activate some parallel pathways that in a second step transmitt signals to PI3Ks by intra-cellular signaling events), such as small GTPases, kinases or phosphatases for example.

Phosphatidylinositol (PtdIns) is the basic building block for the intracellular inositol lipids in eukaryotic cells, consisting of D-myo-inositol-1-phosphate (Ins1P) linked via its phosphate group to diacylglycerol. The inositol head group of PtdIns has five free hydroxy groups and three of these are found to be phosphorylated in cells in different combinations. PtdIns and its phosphorylated derivatives are collectively referred as inositol phospholipids or phosphoinositides (PIs). Eight PI species have been documented in eukaryotic cells (*Vanhaesebroeck et al., 2001, above).* PIs all reside in membranes and are substrates for kinases, phosphatases and lipases.

In vitro, PI3Ks phosphorylate the 3-hydroxyl group of the inositol ring in three different substrates: phosphatidylinositol (PtdIns), phosphatidylinositol-4-phosphate (PI(4)P) and phosphatidylinositol-4,5-biphosphate ($PI(4,5)P_2$), respectively generating three lipid

products, namely phosphatidylinositol 3-monophosphate (PI(3)P), phosphatidylinositol 3,4-bisphosphate ($PI(3,4)P_2$) and phosphatidylinositol 3,4,5-trisphosphate ($PI(3,4,5)P_3$ (see Scheme A below).



Scheme A

The preferred substrate for Class I PI3Ks is $PI(4,5)P_2$. Class II PIKs have a strong prefererence for PtdIns as substrate over PI(4)P and $PI(4,5)P_2$. Class III PI3Ks can only use PtdIns as substrate *in vivo* and are likely to be responsible for the generation of most PI(3)P in cells (*Vanhaesebroeck et al., 2001, above).*

The phosphoinositides intracellular signalling pathway begins with the binding of a signalling molecule (extracellular ligands, stimuli, receptor dimerization, transactivation by heterologous receptor (e.g. receptor tyrosine kinase)) to a G-protein linked transmembrane receptor integrated into the plasma membrane resulting in the activation of PI3Ks.

Once activated, PI3Ks convert the membrane phospholipid $PI(4,5)P_2$ into $PI(3,4,5)P_3$ which in turn can be further converted into another 3' phosphorylated form of phosphoinositides by 5'-specific phosphoinositide phosphatases, thus PI3K enzymatic activity results either directly or indirectly in the generation of two 3'-phosphoinositide sub-types that function as second messengers in intra-cellular signal transduction (*Leslie et al., 2001, Chem. Rev. 101(8) 2365-80; Katso et al., 2001, Annu. Rev. Cell Dev. Biol. 1, 615-75 and Toker et al., 2002, Cell Mol. Life Sci. 59(5) 761-79).*

The role as second messengers of phosphorylated products of PtdIns act is involved in a variety of signal transduction pathways, including those essential to cell proliferation, cell differentiation, cell growth, cell size, cell survival, apoptosis, adhesion, cell motility, cell migration, chemotaxis, invasion, cytoskeletal rearrangement, cell shape changes, vesicle trafficking and metabolic pathway (*Stein, 2000, Mol. Med. Today 6(9) 347-57*). Chemotaxis – the directed movement of cells toward a concentration gradient of chemical attractants, also called chemokines is involved in many important diseases such as inflammation/auto-immunity, neurodegeneration, angiogenesis, invasion/metastasis and wound healing (*Wyman et al., 2000, Immunol Today 21(6) 260-4; Hirsch et al., 2000, Science 287(5455) 1049-53; Hirsch et al., 2001, FASEB J. 15(11) 2019-21 and Gerard et al., 2001, Nat Immunol. 2(2) 108-15*).

PI3-kinase activation, is therefore believed to be involved in a range of cellular responses including cell growth, differentiation and apoptosis (*Parker et al., 1995, Current Biology, 5, 577-99; Yao et al., 1995, Science, 267, 2003-05*).

Recent biochemical studies revealed that, Class I PI3Ks (e.g. Class IB isoform PI3Kγ) are dual-specific kinase enzymes, i.e. they display both lipid kinase activity (phosphorylation of phospho-inositides) as well as protein kinase activity, as they are able to induce the phosphorylation of other protein as substrates, including auto-phosphorylation as intra-molecular regulatory mechanism.

PI3Ks appear to be involved in a number of aspects of leukocyte activation. A p85-associated PI3-kinase activity has been shown to physically associate with the cytoplasmic domain of CD28, which is an important co-stimulatory molecule for the activation of T-cells in response to antigen (*Pages et al., 1994, Nature, 369, 327-29*). These effects are linked to increases in the transcription of a number of genes including interleukin-2 (IL2), an important T cell growth factor (*Fraser et al., 1991, Science, 251, 313-16*). Mutation of CD28 such that it can longer interact with PI3-kinase leads to a failure to initiate IL2 production, suggesting a critical role for PI3-kinase in T cell activation.

Cellular processes in which PI3Ks play an essential role include suppression of apoptosis, reorganization of the actin skeleton, cardiac myocyte growth, glycogen synthase stimulation by insulin, TNFα-mediated neutrophil priming and superoxide generation, and leukocyte migration and adhesion to endothelial cells.

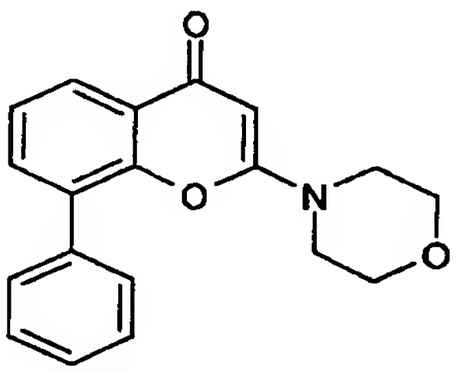
PI3Kγ has been identified as a mediator of G beta-gamma-dependent regulation of JNK activity wherein G beta-gamma are subunits of heterotrimeric G proteins (*Lopez-Ilasaca et al., 1998, J. Biol. Chem. 273(5) 2505-8*).

Recently, it has been described that PI3Kγ relays inflammatory signals through various G(i)-coupled receptors (*Laffargue et al., 2002, Immunity 16(3) 441-51*) and its central to mast cell function, stimuli in context of leukocytes, immunology includes cytokines, chemokines, adenosines, antibodies, integrins, aggregation factors, growth factors, viruses

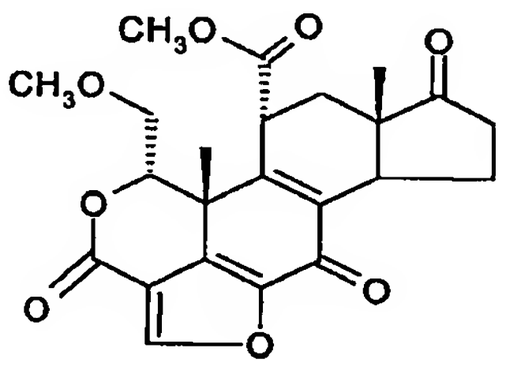
or hormones for example (*Lawlor et al., 2001, J. Cell. Sci., 114 (Pt 16) 2903-1 and Stephens et al., 2002, Curr. Opinion Cell Biol. 14(2), 203-13*).

Specific inhibitors against individual members of a family of enzymes provide valuable tools for deciphering functions of each enzyme.

Two compounds, LY294002 and wortmannin (cf.hereinafter), have been widely used as PI3-kinase inhibitors. These compounds are non-specific PI3K inhibitors, as they do not distinguish among the four members of Class I PI3-kinases.



LY 294002



Wortmannin

IC_{50} values of wortmannin against each of the various Class I PI3-kinases are in the range of 1-10 nM and IC_{50} values for LY294002 against each of these PI3-kinases are about 15-20 μM (*Fruman et al., 1998, Ann. Rev. Biochem., 67, 481-507*), also 5-10 mM on CK2 protein kinase and some inhibitory activity on phospholipases.

Wortmannin is a fungal metabolite which irreversibly inhibits PI3K activity by binding covalently to the catalytic domain of this enzyme. Inhibition of PI3K activity by wortmannin eliminates the subsequent cellular response to the extracellular factor (*Thelen et al., 1994, Proc. Natl. Acad. Sci. USA, 91, 4960-64*). Experiments with wortmannin, show that PI3K activity in cells of hematopoietic lineage, particularly neutrophils, monocytes, and other types of leukocytes, is involved in many of the non-memory immune response associated with acute and chronic inflammation.

Based on studies using wortmannin, there is evidence that PI3-kinase function is also required for some aspects of leukocyte signaling through G-protein coupled receptors (*Thelen et al., 1994*). Morever, it has been shown that wortmannin and LY294002 block neutrophil migration and superoxide release. However, in as much as these compounds do not distinguish among the various isoforms of PI3K, it remains unclear which particular PI3K isoform or isoforms are involved in these phenomena.

Some results have indicated that PI3K inhibitors, for example, LY294002, can increase the in vivo antitumor activity of certain cytotoxic agents (e.g. paclitaxel) (*Grant, 2003, Current Drugs, 6(10), 946-948*).

Recently, 5-phenylthiazole derivatives have been recently developed as PI3K inhibitors (WO 03/072557).

The high relevance of the PI3K pathway in some widely spread diseases stresses the need to develop inhibitors, including selective inhibitors, of PIKs.

Summary of the invention

It is an object of the invention to provide substances which are suitable for the treatment and/or prevention of disorders related to phosphoinositide-3-kinases, PI3Ks.

It is also an object of the present invention to provide substances which are suitable for the treatment and/or prevention of auto-immune and/or inflammatory disorders.

It is also an object of the present invention to provide substances which are suitable for the treatment and/or prevention of cardiovascular diseases.

It is also an object of the present invention to provide substances which are suitable for the treatment and/or prevention of neurodegenerative disorders.

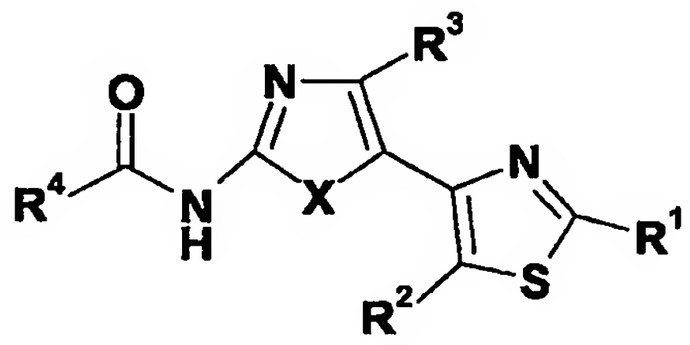
It is also an object of the present invention to provide substances which are suitable for the treatment and/or prevention of a disorder selected from bacterial and viral infections, kidney diseases, platelet aggregation, cancer, transplantation, graft rejection, lung injuries, respiratory diseases and ischemic conditions.

It is notably an object of the present invention to provide chemical compounds which are able to modulate, especially inhibit the activity or function of phosphoinositide-3-kinases, PI3Ks in disease states in mammals, especially in humans.

It is furthermore an object of the present invention to provide a new category of pharmaceutical formulations for the treatment of and/or diseases mediated selected from auto-immune, inflammatory disorders, cardiovascular diseases, neurodegenerative disorders, bacterial and viral infections, kidney diseases, platelet aggregation, cancer, transplantation, graft rejection, lung injuries, respiratory diseases and ischemic conditions.

It is finally an object of the present invention to provide a method for the treatment and/or prevention of disorders selected from auto-immune, inflammatory disorders, cardiovascular diseases, neurodegenerative disorders, bacterial and viral infections, kidney diseases, platelet aggregation, cancer, transplantation, graft rejection or lung injuries, respiratory diseases and ischemic conditions.

In a first aspect, the invention provides thiazole derivatives of Formula (I):



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and X are defined in the detailed description below, for use as a medicament.

In a second aspect, the invention provides a pharmaceutical composition comprising a compound of Formula (I), together with a pharmaceutically acceptable excipient or carrier.

In a third aspect, the invention provides a use of a compound of Formula (I) for the preparation of a pharmaceutical composition useful for a variety of therapies, including alleviating, preventing and/or treating a disrorder selected from auto-immune, inflammatory disorders, cardiovascular diseases, neurodegenerative disorders, bacterial and viral infections, kidney diseases, platelet aggregation, cancer, transplantation, graft rejection or lung injuries, respiratory diseases and ischemic conditions and other diseases and disorders associated with the phosphoinositide-3-kinases, PI3Ks.

In a fourth aspect, the invention provides a method for treating a patient suffering from a disorder selected from auto -immune, inflammatory disorders, cardiovascular diseases, neurodegenerative disorders, bacterial and viral infections, kidney diseases, platelet aggregation, cancer, transplantation, graft rejection or lung injuries, respiratory diseases and ischemic conditions and other diseases and disorders associated with the phosphoinositide-3-kinases, PI3Ks. The method comprises administering a compound according to Formula (I).

Detailed description of the invention:

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly through-out the specification and claims unless an otherwise expressly set out definition provides a broader definition.

"C_1-C_6 -alkyl" refers to monovalent alkyl groups having 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, n-hexyl and the like.

"Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl). Aryl include phenyl, naphthyl, phenantrenyl, benzofuryl and the like.

"C_1-C_6-alkyl aryl" refers to C_1-C_6-alkyl groups having an aryl substituent, including benzyl, phenethyl and the like.

"Heteroaryl" refers to a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, pyrimidinyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadia-zolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxa-zolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnolinyl, napthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl or benzoquinolyl.

"C_1-C_6-alkyl heteroaryl" refers to C_1-C_6-alkyl groups having a heteroaryl substituent, including 2-furylmethyl, 2-thienylmethyl, 2-(1H-indol-3-yl)ethyl and the like.

"C_2-C_6-alkenyl" refers to alkenyl groups preferably having from 2 to 6 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Preferable alkenyl groups include ethenyl (-CH=CH_2), n-2-propenyl (allyl, -CH_2CH=CH_2) and the like.

"C_2-C_6-alkenyl aryl" refers to C_2-C_6-alkenyl groups having an aryl substituent, including 2-phenylvinyl and the like.

"C_2-C_6-alkenyl heteroaryl" refers to C_2-C_6-alkenyl groups having a heteroaryl substituent, including 2-(3-pyridinyl)vinyl and the like.

"C_2-C_6-alkynyl" refers to alkynyl groups preferably having from 2 to 6 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH_2C≡CH), and the like.

"C_2-C_6-alkynyl aryl" refers to C_2-C_6-alkynyl groups having an aryl substituent, including phenylethynyl and the like.

"C_2-C_6-alkynyl heteroaryl" refers to C_2-C_6-alkynyl groups having a heteroaryl substituent, including 2-thienylethynyl and the like.

"C_3-C_8-cycloalkyl" refers to a saturated carbocyclic group of from 3 to 8 carbon atoms having a single ring (*e.g.*, cyclohexyl) or multiple condensed rings (*e.g.*, norbornyl). C_3-C_8-cycloalkyl include cyclopentyl, cyclohexyl, norbornyl and the like.

"Heterocycloalkyl" refers to a C_3-C_8-cycloalkyl group according to the definition above, in which up to 3 carbon atoms are replaced by heteroatoms chosen from the group consisting of O, S, NR, R being defined as hydrogen or methyl. Heterocycloalkyl include pyrrolidine, piperidine, piperazine, 1-methylpiperazine, morpholine, tetrahydrofurane and the like.

"C_1-C_6-alkyl cycloalkyl" refers to C_1-C_6-alkyl groups having a cycloalkyl substituent, including cyclohexylmethyl, cyclopentylpropyl, and the like.

"C_1-C_6-alkyl heterocycloalkyl" refers to C_1-C_6-alkyl groups having a heterocycloalkyl substituent, including 2-(1-pyrrolidinyl)ethyl, morpholinylmethyl, morpholinylethyl, morpholinylpropyl, piperidinylethyl, tetrahydrofuranylmethyl and the like.

"Carboxy" refers to the group –C(O)OH.

"C_1-C_6-alkyl carboxy" refers to C_1-C_6-alkyl groups having an carboxy substituent, including 2-carboxyethyl and the like.

"Acyl" refers to the group –C(O)R where R includes "C_1-C_6-alkyl", "aryl", "heteroaryl", "C_3-C_8-cycloalkyl", "Heterocycloalkyl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"C_1-C_6-alkyl acyl" refers to C_1-C_6-alkyl groups having an acyl substituent, including 2-acetylethyl and the like.

"Aryl acyl" refers to aryl groups having an acyl substituent, including 2-acetylphenyl and the like.

"Heteroaryl acyl" refers to hetereoaryl groups having an acyl substituent, including 2-acetylpyridyl and the like.

"C_3-C_8-(hetero)cycloalkyl acyl" refers to 3 to 8 memebered cycloalkyl or heterocycloalkyl groups having an acyl substituent.

"Acyloxy" refers to the group –OC(O)R where R includes H, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", heterocycloalkyl"heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl acyloxy" refers to C_1-C_6-alkyl groups having an acyloxy substituent, including amino-propionic acid ethyl ester and the like.

"Alkoxy" refers to the group –O-R where R includes "C_1-C_6-alkyl" or "aryl" or "heteroaryl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl". Preferred alkoxy groups include by way of example, methoxy, ethoxy, phenoxy and the like.

"C_1-C_6-alkyl alkoxy" refers to C_1-C_6-alkyl groups having an alkoxy substituent, including methoxy, methoxyethyl and the like.

"Alkoxycarbonyl" refers to the group –C(O)OR where R includes H, "C_1-C_6-alkyl" or "aryl" or "heteroaryl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"C_1-C_6-alkyl alkoxycarbonyl" refers to C_1-C_5-alkyl groups having an alkoxycarbonyl substituent, including 2-(benzyloxycarbonyl)ethyl and the like.

"Aminocarbonyl" refers to the group –C(O)NRR' where each R, R' includes independently hydrogen or C_1-C_6-alkyl or aryl or heteroaryl or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"C_1-C_6-alkyl aminocarbonyl" refers to C_1-C_6-alkyl groups having an aminocarbonyl substituent, including 2-(dimethylaminocarbonyl)ethyl and the like.

"Acylamino" refers to the group –NRC(O)R' where each R, R' is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl acylamino" refers to C_1-C_6-alkyl groups having an acylamino substituent, including 2-(propionylamino)ethyl and the like.

"Ureido" refers to the group –NRC(O)NR'R" where each R, R', R" is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", and where R' and R", together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl ureido" refers to C_1-C_6-alkyl groups having an ureido substituent, including 2-(*N*'-methylureido)ethyl and the like.

"Carbamate" refers to the group –NRC(O)OR' where each R, R' is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"Amino" refers to the group –NRR' where each R,R' is independently hydrogen or "C_1-C_6-alkyl" or "aryl" or "heteroaryl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", or "cycloalkyl", or "heterocycloalkyl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl amino" refers to C_1-C_5-alkyl groups having an amino substituent, including 2-(1-pyrrolidinyl)ethyl and the like.

"Ammonium" refers to a positively charged group –N^+RR'R", where each R,R',R'' is independently "C_1-C_6-alkyl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", or "cycloalkyl", or "heterocycloalkyl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl ammonium" refers to C_1-C_6-alkyl groups having an ammonium substituent, including 2-(1-pyrrolidinyl)ethyl and the like.

"Halogen" refers to fluoro, chloro, bromo and iodo atoms.

"Sulfonyloxy" refers to a group –OSO_2-R wherein R is selected from H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, an –OSO_2-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonyloxy" refers to C_1-C_5-alkyl groups having a sulfonyloxy substituent, including 2-(methylsulfonyloxy)ethyl and the like.

"Sulfonyl" refers to group "–SO_2-R" wherein R is selected from H, "aryl", "heteroaryl", "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, an –SO_2-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonyl" refers to C_1-C_5-alkyl groups having a sulfonyl substituent, including 2-(methylsulfonyl)ethyl and the like.

"Sulfinyl" refers to a group "–S(O)-R" wherein R is selected from H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, a –SO-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfinyl" refers to C_1-C_5-alkyl groups having a sulfinyl substituent, including 2-(methylsulfinyl)ethyl and the like.

"Sulfanyl" refers to groups –S-R where R includes H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, a –SO-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl

heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl". Preferred sulfanyl groups include methylsulfanyl, ethylsulfanyl, and the like.

"C_1-C_6-alkyl sulfanyl" refers to C_1-C_5-alkyl groups having a sulfanyl substituent, including 2-(ethylsulfanyl)ethyl and the like.

"Sulfonylamino" refers to a group –$NRSO_2$-R' where each R, R' includes independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonylamino" refers to C_1-C_5-alkyl groups having a sulfonylamino substituent, including 2-(ethylsulfonylamino)ethyl and the like.

"Aminosulfonyl" refers to a group –SO_2-NRR' where each R, R' includes independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl aminosulfonyl" refers to C_1-C_6-alkyl groups having an aminosulfonyl substituent, including 2-(cyclohexylaminosulfonyl)ethyl and the like.

"Substituted or unsubstituted": Unless otherwise constrained by the definition of the individual substituent, the above set out groups, like "alkenyl", "alkynyl", "aryl", "heteroaryl", "cycloalkyl", "heterocycloalkyl" etc. groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "cycloalkyl", "heterocycloalkyl", "C_1-C_6-alkyl aryl", "C_1-C_6-alkyl heteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", "amino", "ammonium", "acyl", "acyloxy", "acylamino", "aminocarbonyl", "alkoxycarbonyl", "ureido", "aryl", "carbamate", "heteroaryl", "sulfinyl", "sulfonyl", "alkoxy", "sulfanyl", "halogen", "carboxy", trihalomethyl, cyano, hydroxy, mercapto, nitro, and the like.

"Substituted" refers to groups substituted with from 1 to 5 substituents selected from the group consisting of "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "cycloalkyl", "heterocycloalkyl", "C_1-C_6-alkyl aryl", "C_1-C_6-alkyl heteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", "amino", "aminosulfonyl", "ammonium", "acyl amino", "amino carbonyl", "aryl", "heteroaryl", "sulfinyl", "sulfonyl", "alkoxy", "alkoxy carbonyl", "carbamate", "sulfanyl", "halogen", trihalomethyl, cyano, hydroxy, mercapto, nitro, and the like

"Pharmaceutically acceptable cationic salts or complexes" is intended to define such salts as the alkali metal salts, (e.g. sodium and potassium), alkaline earth metal salts (e.g. calcium or magnesium), aluminium salts, ammonium salts and salts with organic amines such as with methylamine, dimethylamine, trimethylamine, ethylamine, triethylamine, morpholine, N-Me-D-glucamine, N,N'-bis(phenylmethyl)-1,2-ethanediamine, ethanolamine, diethanolamine, ethylenediamine, N-methylmorpholine, piperidine, benzathine (N,N'-dibenzylethylenediamine), choline, ethylene-diamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, thromethamine (2-amino-2-hydroxymethyl-1,3-propanediol), procaine as well as amines of formula –NR,R',R'' wherein R, R', R'' is independently hydrogen, alkyl or benzyl. Especially preferred salts are sodium and potassium salts.

"Pharmaceutically acceptable salts or complexes" refers to salts or complexes of the below-identified compounds of Formula (I) that retain the desired biological activity. Examples of such salts include, but are not restricted to acid addition salts formed with inorganic acids (*e.g.,* hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene sulfonic acid, naphthalene disulfonic acid, and poly-galacturonic acid. Said compounds can also be administered as pharmaceutically acceptable quaternary salts known by a person skilled in the art, which

specifically include the quarternary ammonium salt of the formula –NR,R',R" $^{+}$ Z^{-}, wherein R, R', R" is independently hydrogen, alkyl, or benzyl, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkyl aryl, C_1-C_6-alkyl heteroaryl, cycloalkyl, heterocycloalkyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, cinnamoate, mandeloate, and diphenylacetate).

"Pharmaceutically active derivative" refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the activity disclosed herein.

It has now been found that compounds of the present invention are modulators of the Phosphatoinositides 3-kinases (PI3Ks). When the phosphatoinositides 3-kinase (PI3K) enzyme is inhibited by the compounds of the present invention, PI3K is unable to exert its enzymatic, biological and/or pharmacological effects. The compounds of the present invention are therefore useful in the treatment and prevention of autoimmune disorders and/or inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, kidney diseases, platelet aggregation, cancer, transplantation, graft rejection or lung injuries.

General Formula (I) according to the present invention also comprises its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof. Preferred pharmaceutically acceptable salts of the Formula (I) are acid addition salts formed with pharmaceutically acceptable acids like hydrochloride, hydrobromide, sulfate or bisulfate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzenesulfonate, and *para*-toluenesulfonate salts.

The compounds according to Formula (I) are suitable for the modulation, notably the inhibition of the activity of phosphatoinositides 3-kinases (PI3K). It is therefore believed

that the compounds of the present invention are also particularly useful for the treatment and/or prevention of disorders which are mediated by PI3Ks, particularly PI3Kγ. Said treatment involves the modulation – notably the inhibition or the down regulation – of the phosphatoinositides 3-kinases.

The compounds according to Formula (I) are suitable for use as a medicament.

In one embodiment, the invention provides thiazole derivatives of Formula (I) wherein R^1 is selected from $-NR^5R^6$ and $-SO_2R^7$;

R^2, R^3 and R^5 are selected independently from H, optionally substituted C_1-C_6-alkyl, including methyl, optionally substituted C_2-C_6-alkenyl and optionally substituted C_2-C_6-alkynyl;

R^4 is selected from H, optionally substituted C_1-C_6-alkyl, including methyl and ethyl, optionally substituted C_2-C_6-alkenyl and optionally substituted C_2-C_6-alkynyl and NR^8R^9 wherein R^8 and R^9 are independently selected from H, optionally substituted C_1-C_6-alkyl, optionally substituted C_2-C_6-alkenyl, optionally substituted C_2-C_6-alkynyl and optionally substituted C_1-C_6-alkyl acyloxy, including amino-propionic acid ethyl ester;

R^6 is selected from optionally substituted C_1-C_6-alkyl, including t-butyl, optionally substituted C_2-C_6-alkenyl, including allyl, C_2-C_6-alkynyl, optionally substituted C_1-C_6-alkyl alkoxy, including methoxyethyl, optionally substituted aryl, including optionally substituted phenyl such as phenyl, methoxy phenyl, ethoxy phenyl, methylphenyl, acetylamino phenyl, amino phenyl, dimethylamino phenyl, nitro phenyl, benzoic acid, ethyl phenyl, methylphenyl, bromophenyl, chlorophenyl, cyanophenyl, aminosulfonyl phenyl, dimethoxy phenyl, acetyl phenyl, hydroxy phenyl, benzyl piperazine carbonyl phenyl, dimethylpyrimidin amino sulfonyl phenyl, dimethoxypyrimidin amino sulfonyl phenyl, methylisoxazol amino sulfonyl phenyl and optionally substituted fused phenyl such as benzofuran, optionally substituted heteroaryl, including optionally substituted pyridin such as pyridin, methoxy pyridin, chloro pyridin, optionally substituted C_3-C_8-cycloalkyl,

including cyclohexyl, optionally substituted C_3-C_8-heterocycloalkyl, optionally substituted aryl C_1-C_6-alkyl, including benzyl, phenyl ethyl and 2-hydroxy-2-phenyl ethyl, optionally substituted heteroaryl C_1-C_6-alkyl, optionally substituted C_3-C_8-cycloalkyl C_1-C_6-alkyl and optionally substituted C_3-C_8-heterocycloalkyl C_1-C_6-alkyl, including tetrahydofuran methyl, 3-morpholin-4-yl-propyl and piperidin ethyl; or alternatively R^5 and R^6, together with the carbon atoms they are linked to, form an optionally substituted 5-8-membered saturated, partially unsaturated or aromatic ring containing optionally one or more heteroatoms selected from O, N and S, including optionally substituted piperidin, such as piperidin, piperidin carboxylate, hydroxyethyl piperidin, optionally substituted pyrrolidin, including pyrrolidin, hydroxypyrrolidin and morpholinyl;

R^7 is selected from optionally substituted C_1-C_6-alkyl, optionally substituted C_2-C_6-alkenyl, optionally substituted C_2-C_6-alkynyl and $NR^{10}R^{11}$ wherein R^{10} and R^{11} are independently selected from H, optionally substituted C_1-C_6-alkyl, optionally substituted C_2-C_6-alkenyl and optionally substituted C_2-C_6-alkynyl; or alternatively R^{10} and R^{11}, together with the carbon atoms they are linked to, form an optionally substituted 5-8-membered saturated, partially unsaturated or aromatic ring containing optionally one or more heteroatoms selected from O, N and S;

X is selected from O and S; as well as isomers and mixtures of these for use as a medicament.

In a specific embodiment, the invention provides thiazole derivatives of Formula (I) wherein R^1 is selected from $-NR^5R^6$.

In another specific embodiment, the invention provides thiazole derivatives of Formula (I) wherein R^2 is H.

In another specific embodiment, the invention provides thiazole derivatives of Formula (I) wherein R^3 is methyl.

In another specific embodiment, the invention provides thiazole derivatives wherein R^4 is selected from optionally substituted C_1-C_6-alkyl, optionally substituted C_2-C_6-alkenyl and optionally substituted C_2-C_6-alkynyl.

In another specific embodiment, the invention provides thiazole derivatives wherein R^5 is H and R^6 is selected from optionally substituted C_1-C_6-alkyl, optionally substituted C_2-C_6-alkenyl, optionally substituted C_2-C_6-alkynyl, optionally substituted C_1-C_6-alkyl alkoxy, optionally substituted C_3-C_8-cycloalkyl C_1-C_6-alkyl and optionally substituted C_3-C_8-heterocycloalkyl C_1-C_6-alkyl.

In another specific embodiment, the invention provides thiazole derivatives wherein wherein R^5 is H and R^6 is selected from optionally substituted aryl C_1-C_6-alkyl and optionally substituted heteroaryl C_1-C_6-alkyl.

In another specific embodiment, the invention provides thiazole derivatives wherein R^5 is H and R^6 is selected from optionally substituted aryl and optionally substituted heteroaryl.

In another specific embodiment, the invention provides thiazole derivatives wherein R^5 and R^6, together with the carbon atoms they are linked to, form an optionally substituted 5-8-membered saturated, partially unsaturated or aromatic ring containing optionally one or more heteroatoms selected from O, N and S.

In another specific embodiment, the invention provides thiazole derivatives wherein R^5 and R^6, together with the carbon atoms they are linked to, form an optionally substituted 5-8-membered saturated ring optionally additionally containing an oxygen atom.

In another specific embodiment, the invention provides bis-thiazole derivatives, i.e. thiazole derivatives of Formula (I) wherein X is S.

Compounds of the present invention include in particular those of the group consisting of:

Example N°	Name
1	3-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}benzoic acid
2	4-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}benzoic acid
3	N-[2-(benzylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide
4	N-{4-methyl-2-[(2-phenylethyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide
5	N-(4-methyl-2-piperidin-1-yl-4,5-bi-1,3-thiazol-2-yl)acetamide
6	N-[2-(allylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide
7	N-[4-methyl-2-(pyridin-3-ylamino)-4,5-bi-1,3-thiazol-2-yl]acetamide
8	N-[4-methyl-2-(pyridin-2-ylamino)-4,5-bi-1,3-thiazol-2-yl]acetamide
9	N-{2-[(4-methoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
10	N-{2-[(4-hydroxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
11	N-{4-methyl-2-[(4-nitrophenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide
12	4-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}benzamide
13	N-[2-({4-[(4-benzylpiperazin-1-yl)carbonyl]phenyl}amino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide

Example N°	Name
14	N-(2-amino-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide
15	N-(2-anilino-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide
16	N-(4-methyl-2-morpholin-4-yl-4,5-bi-1,3-thiazol-2-yl)acetamide
17	N-[4-methyl-2-(4-methylpiperazin-1-yl)-4,5-bi-1,3-thiazol-2-yl]acetamide
18	Methyl 1-[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]piperidine-3-carboxylate
19	N-{2-[4-(2-hydroxyethyl)piperidin-1-yl]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
20	N-(4-methyl-2-pyrrolidin-1-yl-4,5-bi-1,3-thiazol-2-yl)acetamide
21	N-[2-(3-hydroxypyrrolidin-1-yl)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide
22	N-[2-(tert-butylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide
23	N-{2-[(6-methoxypyridin-3-yl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
24	N-{2-[(6-chloropyridin-3-yl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
25	N-{2-[(4-cyanophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
26	N-{2-[(4-chlorophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide

Example N°	Name
27	N-{2-[(2-chlorophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
28	N-{2-[(2-methoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
29	N-{2-[(3-chlorophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
30	N-{2-[(3-hydroxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
31	N-{4-methyl-2-[(2-morpholin-4-ylethyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide
32	N-{4-methyl-2-[(2-piperidin-1-ylethyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide
33	N-{2-[(2-methoxyethyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
34	N-[2-(cyclohexylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide
35	N-{4-methyl-2-[(3-morpholin-4-ylpropyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide
36	N-{4-methyl-2-[(tetrahydrofuran-2-ylmethyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide
37	N-{2-[(2-hydroxy-2-phenylethyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide
38	N-[2-(1-benzofuran-5-ylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide
39	N-{2-[(3-cyanophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide

Example N°	Name
40	[4-methyl-2-(pyridin-3-ylamino)-4,5-bi-1,3-thiazol-2-yl]formamide
41	Ethyl N-({[2-(allylamino)-4-methyl-4,5'-bi-1,3-thiazol-2-yl]amino}carbonyl)-beta-alaninate
42	N-{4-methyl-5-[2-(pyridin-3-ylamino)-1,3-thiazol-4-yl]-1,3-oxazol-2-yl}acetamide

N-{2-[(4-ethoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(4-methylphenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(4-{[(4,6-dimethylpyrimidin-2-yl)amino]sulfonyl}phenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-[2-(allylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]propanamide;

N-{2-[(4-{[(2,6-dimethoxypyrimidin-4-yl)amino]sulfonyl}phenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)amino]-4,5-bi-1,3-thiazol-2-yl}propanamide;

N-{2-[(4-{[(4,6-dimethylpyrimidin-2-yl)amino]sulfonyl}phenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}propanamide;

N-(4-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}phenyl)acetamide;

N-{4-methyl-2-[(3-nitrophenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(4-aminophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(2-ethylphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(2-methylphenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(4-bromophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-(2-{[4-(aminosulfonyl)phenyl]amino}-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide;

N-{2-[(2,5-dimethoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(3-acetylphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-(2-{[4-(dimethylamino)phenyl]amino}-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide.

The compounds of the present invention are useful as medicaments. They may be used for the preparation of a medicament for the prophylaxis and/or treatment of autoimmune disorders and/or inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, kidney diseases, platelet aggregation, cancer, transplantation, graft rejection or lung injuries.

In one embodiment, the compounds of Formula (I) are useful for the treatment and/or prophylaxis of autoimmune diseases or inflammatory diseases such as multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, lung inflammation, thrombosis or brain infection/inflammation such as meningitis or encephalitis.

In another embodiment, the compounds of Formula (I) are useful for the treatment and/or prophylaxis of neurodegenerative diseases including multiple sclerosis, Alzheimer's disease, Huntington's disease, CNS trauma, stroke or ischemic conditions.

In still a further embodiment according to the invention, the compounds of Formula (I) are useful for the treatment and/or prophylaxis of cardiovascular diseases such as atherosclerosis, heart hypertrophy, cardiac myocyte dysfunction, elevated blood pressure or vasoconstriction.

In still another embodiment according to the invention, the compounds of Formula (I) are useful for the treatment and/or prophylaxis of chronic obstructive pulmonary disease, anaphylactic shock fibrosis, psoriasis, allergic diseases, asthma, stroke or ischemic conditions, ischemia-reperfusion, platelets aggregation/activation, skeletal muscle atrophy/hypertrophy, leukocyte recruitment in cancer tissue, angiogenesis, invasion metastisis, in particular melanoma, Karposi's sarcoma, acute and chronic bacterial and viral

infections, sepsis, transplantation, graft rejection, glomerulo sclerosis, glomerulo nephritis, progressive renal fibrosis, endothelial and epithelial injuries in the lung or in general lung airways inflammation.

The thiazole derivatives exemplified in this invention may be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred experimental conditions (i.e. reaction temperatures, time, moles of reagents, solvents etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by the person skilled in the art, using routine optimisation procedures.

Synthesis of compounds of the invention:

The novel bis-thiazole or oxazole-thiazole derivatives according to Formula (I) can be prepared from readily available starting materials by several synthetic approaches, using both solution-phase and solid-phase chemistry protocols (*Pirrung et al., J. Comb. Chem. 2001, 3, 90-96*).Examples of synthetic pathways for the will be described.

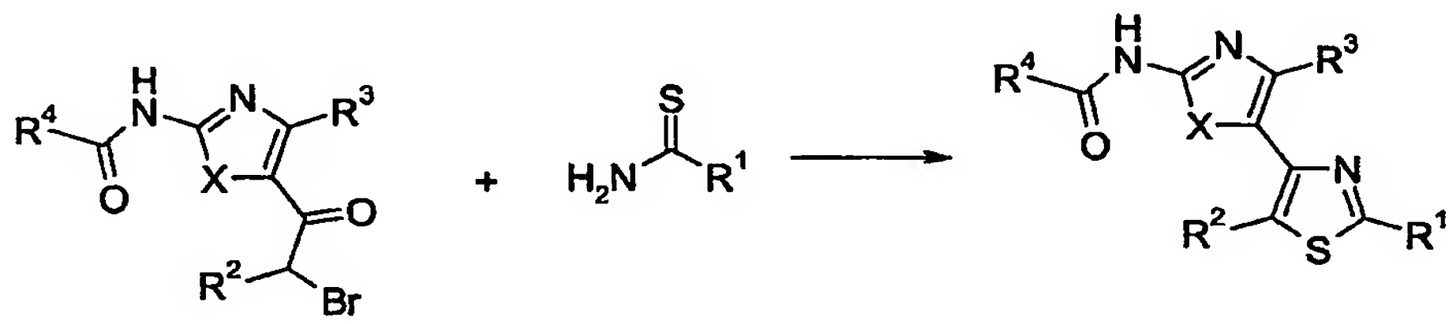
The following abbreviations refer respectively to the definitions below:

min (minute), **hr** (hour), **g** (gram),), **MHz** (Megahertz), **ml** (milliliter), **mmol** (millimole), **mM** (millimolar), **rt** (room temperature), **ATP** (Adenoside Triphosphate), **BSA** (Bovine Serum Albumin), **CDI** (N,N'-carbonyldiimidazole), **DCM** (dichloromethane), **DCC** (dicyclohexylcarbodiimide), **DIEA** (di-isopropyl ethylamine), **DMSO** (Dimethyl Sulfoxide), **EDC** (1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydro-chloride), **HPLC** (High Performance Liquid Chromatography), **Ins1P** (D-myo-inositol-1-phosphate), **mCPBA** (*m*-chloroperoxybenzoic acid), **MS** (mass spectrometry), **NMR** (Nuclear Magnetic Resonance), **PBS** (Phosphate Buffered Saline), **PIs** (Phosphoinositides), **PI3Ks** (Phosphoinositide 3-kinases), **PI(3)P** (Phosphatidylinosit ol 3-monophosphate), **PI(3,4)P_2** (Phosphatidylinositol 3,4-bisphosphate), **PI(3,4,5)P_3** (Phosphatidylinositol 3,4,5-

trisphosphate), **PI(4)P** (Phosphatidylinositol-4-phosphate), **PI(4,5)P_2)** (Phosphatidylinositol-4,5-biphosphate), **PtdIns** (Phosphatidylinositol), **SPA** (Scintillation Proximity Assay), **TEA** (triethylamine), **THF** (tetrahydrofuran), **TLC** (Thin Layer Chromatography), **UV** (Ultraviolet).

One synthetic approach (Scheme 1 below) consists in reacting approximately equimolar amounts of an α-bromoketone reactant (P1) with a thiourea, a dithiocarbamate or a dithiocarbamic acid alkyl, alkenyl or alkynyl ester (P2), mixed in a solvent, preferably polar such as alcoholic solvent, to afford a compound of Formula (I). The temperature of the reaction depends on the nature of (P1) and (P2), ranging between –20°C and reflux.

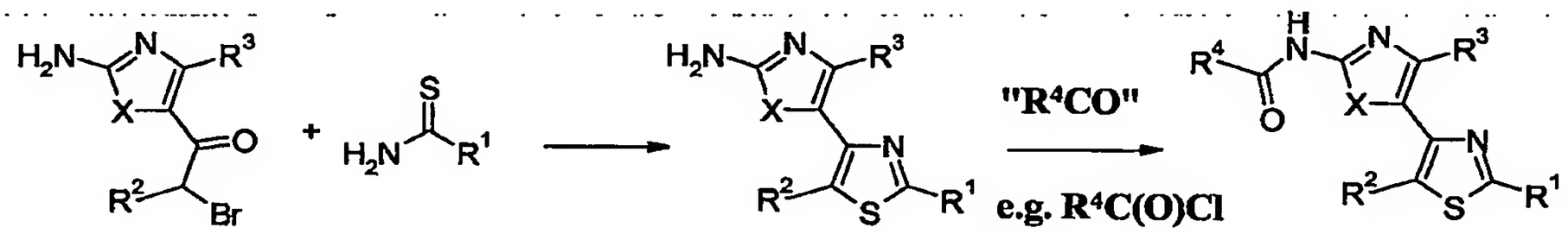
Scheme 1



P1 **P2** **(I)**

Another synthetic approach, described on Scheme 2 below, consists in reacting in the same way a free amine derivative (P1a), with a thiourea or a dithiocarbamate (P2), affording the corresponding bis-thiazole or oxazole-thiazole of Formula (Ia).

Scheme 2



P1a **P2** **Ia** **(I)**

Derivative (Ia) can be further substituted by a group $-C(O)R^4$ to lead to a compound of Formula (I) using conditions known by the person skilled in the art.

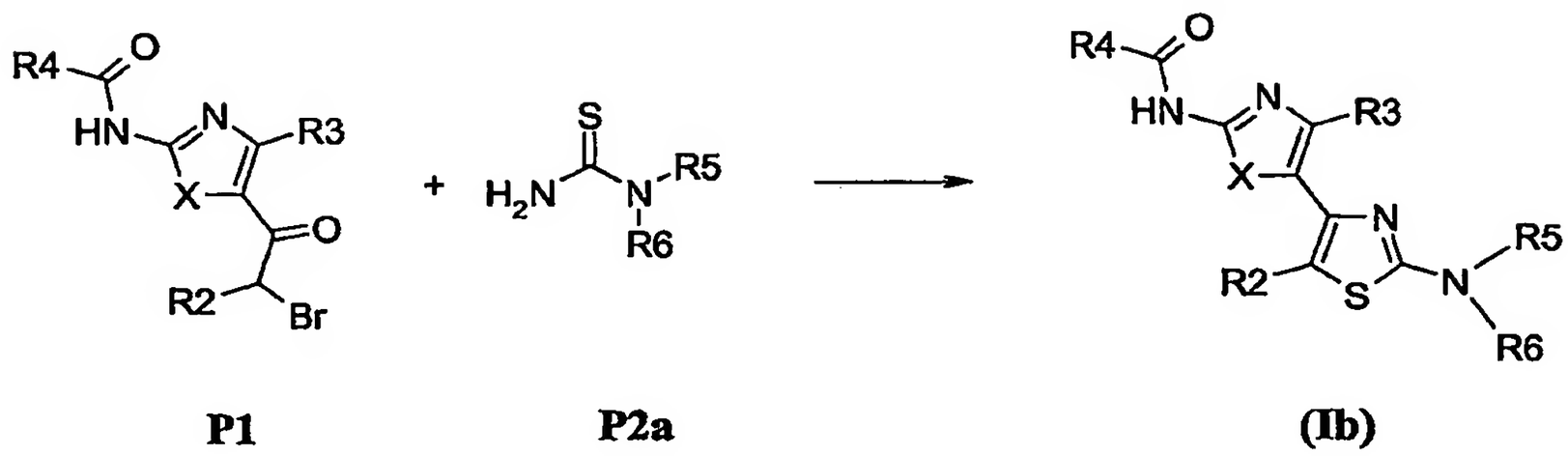
When the group $-C(O)R^4$ is an acyl group, the corresponding acyl chloride is added to intermediate (Ia) in the presence of a base, e.g. pyridine, DIEA, TEA, etc. The corresponding carboxylic acid can be also added in the presence of an activating agent such as DCC, EDC, etc.

A formyl group, i.e. $-C(O)R^4 = -C(O)H$, can be introduced by heating intermediate (Ia) in formic acid or in any alkyl formate, with or without a cosolvent. A substituted urea is formed by addition of an isocyanate, $R^8R^9NC(O)$, to intermediate (Ia) in the presence of a base, e.g. DIEA, TEA, etc. The sequential addition of CDI and ammonia to intermediate (Ia) affords a compound of Formula (I) with $-C(O)R^4 = -C(O)NH_2$.

Other $-C(O)R^4$ functionalities can be added to intermediate (Ia), to give a compound of Formula (I) as defined above in the description, using reaction conditions known to the person skilled in the art.

In the case of compounds of the invention of Formula (I) wherein $R^1 = NR^5R^6$, i.e. of Formula (Ib), the same processes as described above may be used and wherein derivatives of formula (P2) are thiourea of formula (P2a) (Scheme 3 below).

Scheme 3



P1 **P2a** **(Ib)**

For the preparation of compounds of Formula (Ib), approximately equimolar amounts of the α-bromoketone reactant (P1) and N-substituted thiourea (P2a) are stirred as a solution or a suspension in a solvent, preferably polar such as alcoholic solvent. When reagents (P1) or (P2a) are used as salt, an excess of base, preferably triethylamine or pyridine (about 3 equivalents), is added to the reaction mixture. The temperature chosen for this reaction depends on the nature of (P1) and (P2a), varying between –20°C and reflux.

The desired bis-thiazole or oxazole-thiazole of Formula (Ib) is then isolated as HBr salt by filtration, in case it precipitates out of the reaction mixture upon cooling, or by evaporation of the solvents to obtain the crude product. This crude product can be then purified, if desired, e.g. by crystallization or by standard chromatographic methods. When R^5 and R^6 form a ring, the same processes as described above may be used.

Alternatively the HBr liberated during the reaction can be first neutralized by addition of an excess of base, preferably triethylamine or pyridine (about 3 equivalents). The desired bis-thiazole or oxazole-thiazole of Formula (Ib) is then isolated by filtration, in case it precipitates out of the reaction mixture upon cooling, and washed with water to remove the HBr salt of the base added. It can also be precipitated by addition of water and isolated by filtration or be extracted with an organic solvents, such as EtOAc or DCM. The resulting crude product can be then purified, if desired, e.g. by crystallization or by standard chromatographic methods.

These reaction conditions described above and detailed in the Examples below can be also applied on when using compounds (P1a) as starting material. In this case, compounds of Formula (Ib) can be then obtained with an additional step for the introduction of the group $-C(O)R^4$, as defined above in the description, using conditions known to the person skilled in the art.

When $-C(O)R^4$ is an acyl group, the corresponding acyl chloride is added to intermediate (Ia), wherein $R^1 = NR^5R^6$, in the presence of a base, e.g. pyridine, DIEA, TEA, etc. The corresponding carboxylic acid can also be added in the presence of an activating agent such as DCC, EDC, etc.

A formyl group, i.e. $-C(O)R^4 = -C(O)H$, can be introduced by heating (Ia), wherein $R^1 = NR^5R^6$, in formic acid or in any alkyl formate with or without a cosolvent. A substituted urea is formed by addition of an isocyanate, $R^8R^9NC(O)$, to intermediate (Ia), wherein $R^1 = NR^5R^6$, in the presence of a base, e.g. DIEA, TEA, etc. The sequential addition of CDI and ammonia to intermediate (Ia), wherein $R^1 = NR^5R^6$, affords compound of the invention according to Formula (Ib) with $-C(O)R^4 = -C(O)NH_2$.

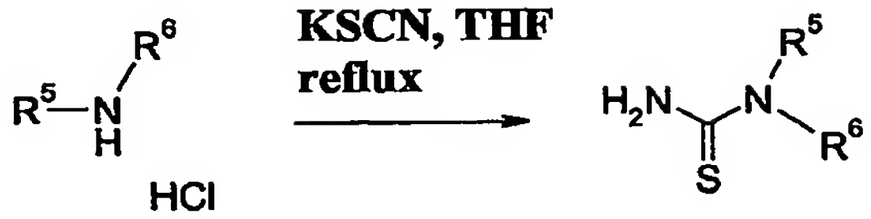
Other $-C(O)R^4$ functionalities can be added to intermediate (Ia), wherein $R^1 = NR^5R^6$, to give a compound of the invention according to Formula (Ib) as defined above in the description, using reaction conditions known to the person skilled in the art.

Thioureas (P2a) used in synthetic Sheme 3 above are either commercially available from various sources or synthesized using conditions known to the person skilled in the art.

For example, thioureas (P2a) can be obtained by coupling a salt of an amine NHR^5R^6, preferably HCl salt, with potassium thiocyanate used in equimolarity in THF under reflux (*Herr et al., J. Synthesis, 2000, 1569-1574*) as shown on Scheme 4 below, Pathway A.

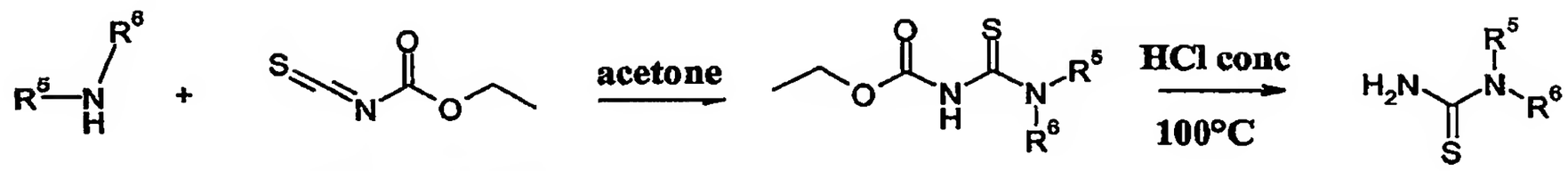
Scheme 4

Pathway A



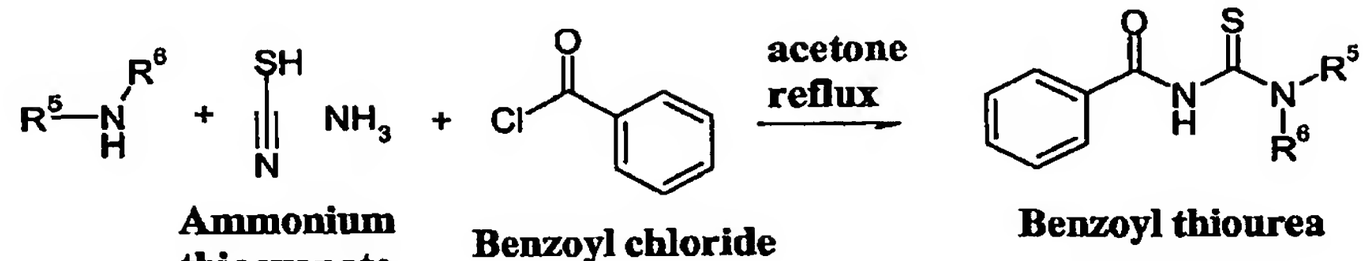
P2a

Pathway B

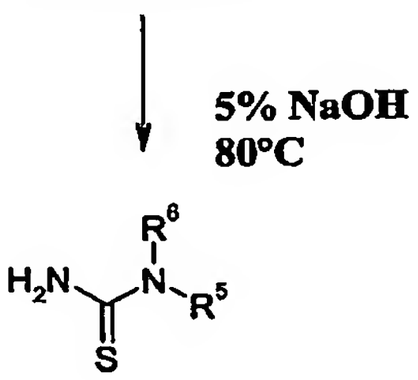


P2a

Pathway C

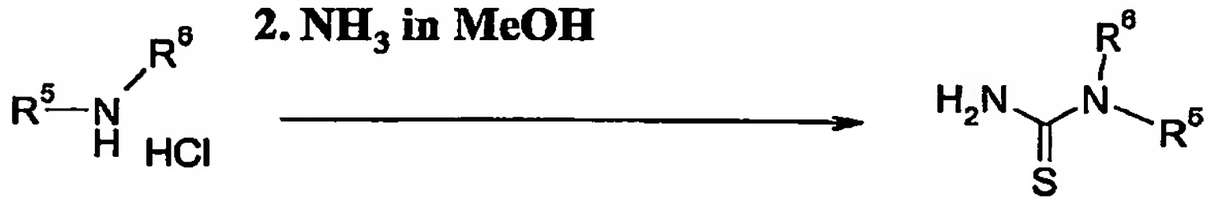


Ammonium thiocyanate **Benzoyl chloride** **Benzoyl thiourea**



P2a

Pathway D



P2a

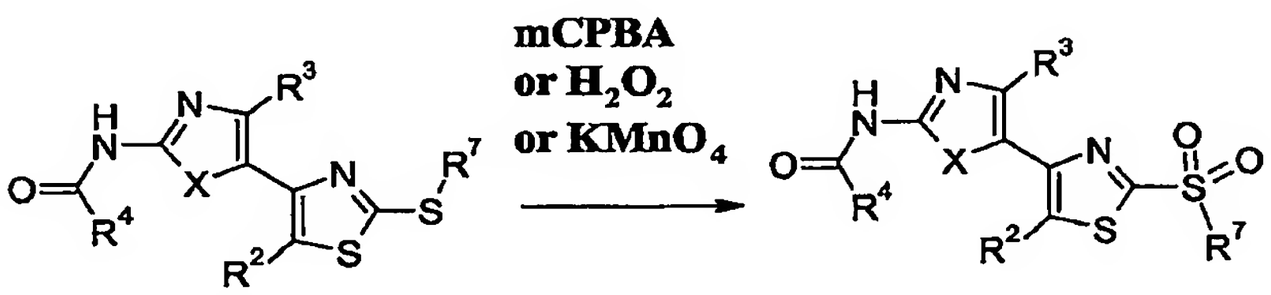
The amine NHR^5R^6 can be first activated with ethoxycarbonyl isothiocyanate affording an ethoxycarbonyl thiourea intermediate, as presented above on Scheme 4, Pathway B (*Hartmann et al., Prakt. Chem. 1973, 315, 144-148*). Upon deprotection under acidic conditions, e.g. concentrated HCl, the desired thiourea (P2a) is released. The amine NHR^5R^6 can be also activated with benzoyl isothiocyanate, obtained by addition of benzoyl chloride to ammonium thiocyanate, giving a benzoyl thiourea intermediate, as shown above on Scheme 4, Pathway C (*Rasmussen et al., Synthesis, 1988, 456-459*). Upon deprotection under basic conditions, e.g. NaOH, the desired thiourea (P2a) is released. Alternatively, the amine NHR^5R^6 can be reacted with thiophogene, followed by the addition of ammonia, as presented above on Scheme 4, Pathway D (*Wilson et al., J. Bioorg. Med. Chem. Lett. 2001, 11, 915-918; Feldman et al., Tetrahedron Lett. 1991, 32, 875*). If the above set of synthetic methods are not applicable to obtain N-substituted thiourea (P2a), suitable methods of preparation known by a person skilled in the art should be used.

The thioureas (P2a) synthesized under conditions described in pathways A, B, C and D, or any other method reported in the literature, are either used directly in the synthesis of bis-thiazole or oxazole-thiazole of Formula (I) or first purified, if desired, e.g. by crystallization or by standard chromatographic methods.

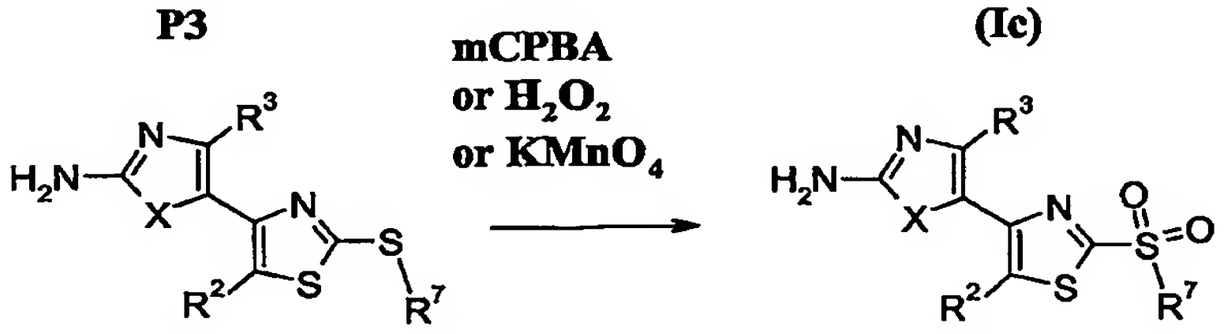
Bis-thiazole or oxazole-thiazole derivatives of the invention according to Formula (I) wherein R^1 is SO_2R^7, i.e. compounds of Formula (Ic), can be obtained by several synthetic approaches. An example of such a process is described hereinafter.

Bis-thiazole or oxazole-thiazole derivatives of the invention according to Formula (I) wherein R^1 is SO_2R^7, i.e. compounds of Formula (Ic) and wherein R^7 is selected from optionally substituted C_1-C_6-alkyl, optionally substituted C_2-C_6-alkenyl and optionally substituted -alkynyl can be obtained by the oxidation of the corresponding alkyl, alkenyl or alkynyl sulfure (P3) as shown below on Scheme 5 below.

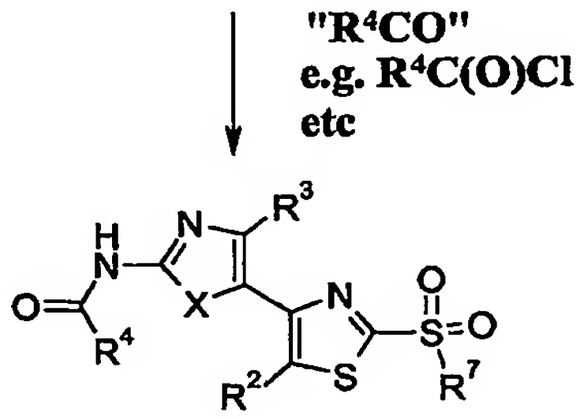
Scheme 5



P3 **(Ic)**



P3a **Id**



(Ic)

Oxidative agents used in this transformation can be selected from *m*-chloroperoxybenzoic acid, mCPBA, (*Alvarez-Ibarra et al., Heterocycles 1991, 32, 2127-2137*), $KMnO_4$ (*Konno*

et al., Yakugaku ***1990****, 110,105-114*), H_2O_2 (*Fukatsu et al., Heterocycles, **1989**, 29, 1517-1528*) and any other oxidative agents known by the person skilled in the art.

The oxidation reaction can also be performed on the free amine (P3a) to lead to the corresponding bis-thiazole or oxazole-thiazole intermediate (Id) that can be further substituted by a group $-C(O)R^4$ into a compound of the invention of Formula (Ic), using conditions known to the person skilled in the art.

When $-C(O)R^4$ is an acyl group, the corresponding acyl chloride is added to intermediate (Id) in the presence of a base, e.g. pyridine, DIEA, TEA, etc. The corresponding carboxylic acid can be also added in the presence of an activating agent such as DCC, EDC, etc.

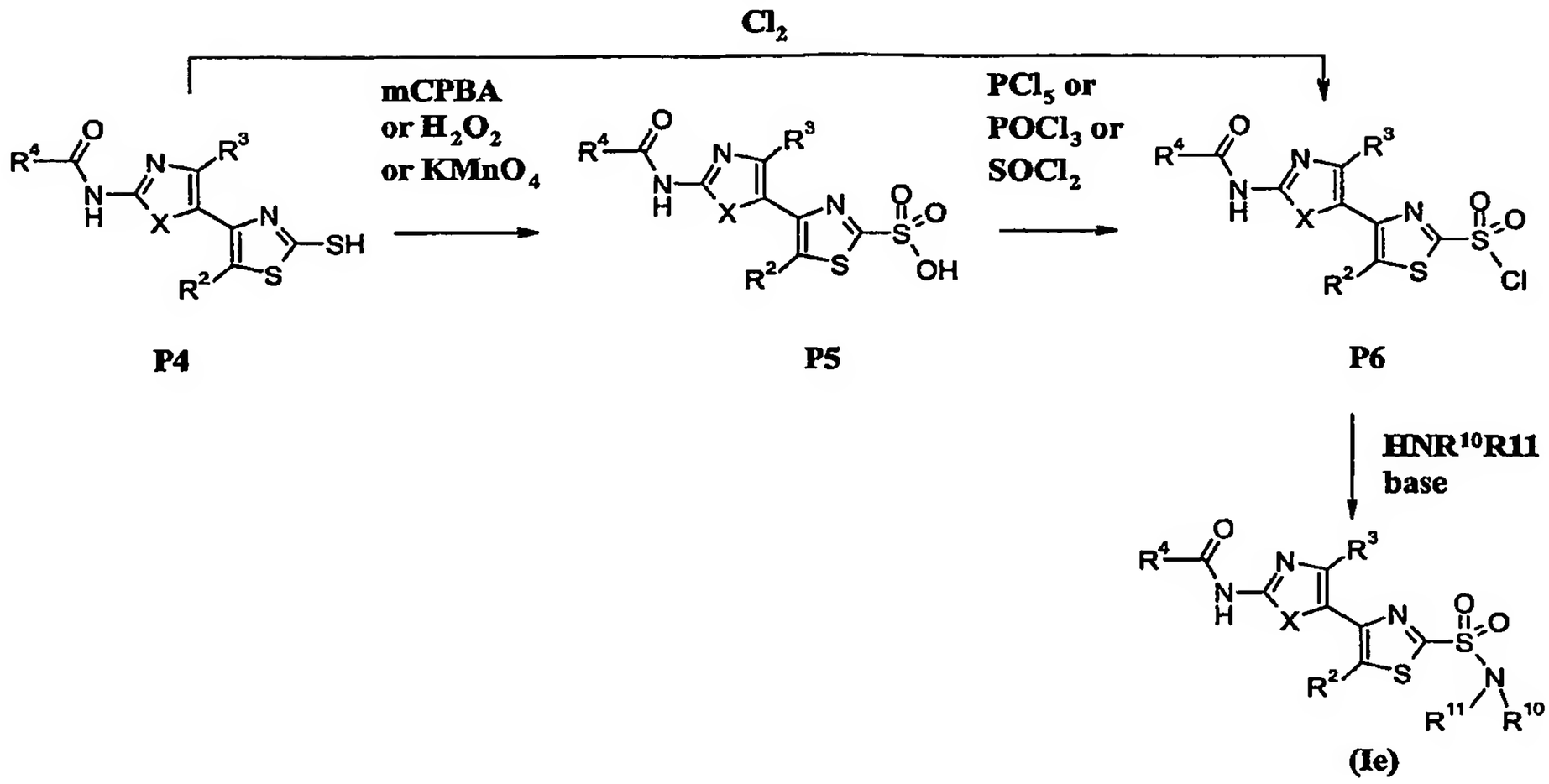
A formyl group, $-C(O)R^4 = -C(O)H$, can be introduced by heating intermediate (Id) in formic acid or in any alkyl formate, with or without a cosolvent. A substituted urea is formed by addition of an isocyanate, $R^8R^9NC(O)$, to intermediate (Id) in the presence of a base, e.g. DIEA, TEA, etc. The sequential addition of CDI and ammonia to intermediate (Id) affords a compound of the invention of Formula (Ic) with $-C(O)R^4 = -C(O)NH_2$.

Other $-C(O)R^4$ functionalities can be added to intermediate (Id), to lead to a compound of the invention according to Formula (Ic) as defined above in the description, using reaction conditions known to the person skilled in the art.

Bis-thiazole or oxazole-thiazole derivatives of the invention according to Formula (I) wherein R^1 is $-SO_2NR^{10}R^{11}$, i.e. compounds of Formula (Ie) can be obtained in two steps, starting with an oxidative chlorination step with Cl_2 for the transformation of a sulfure derivative (P4) into the corresponding sulfonyl chloride (P6) as shown on Scheme 6 below.

The second step is the addition of a suitable amine $HNR^{10}R^{11}$ to the sulfonyl chloride (P6) in the presence of a base, e.g. DIEA, TEA, pyridine, etc, affording sulfonamide derivatives of the invention according to Formula (Ie), as shown on Scheme 6 below. When R^{10} and R^{11} form a ring, the same processes as described above may be used.

Scheme 6



The oxidative chlorination step can be replaced by a two steps process, involving the oxydation of a sulfure (P4) into the corresponding sulfonic acid (P5) (*Mazzone et al. Il Farmaco Ed. Sc. 1980, 36, 181-196*), followed by its chlorination into a sulfonyl chloride (P6).

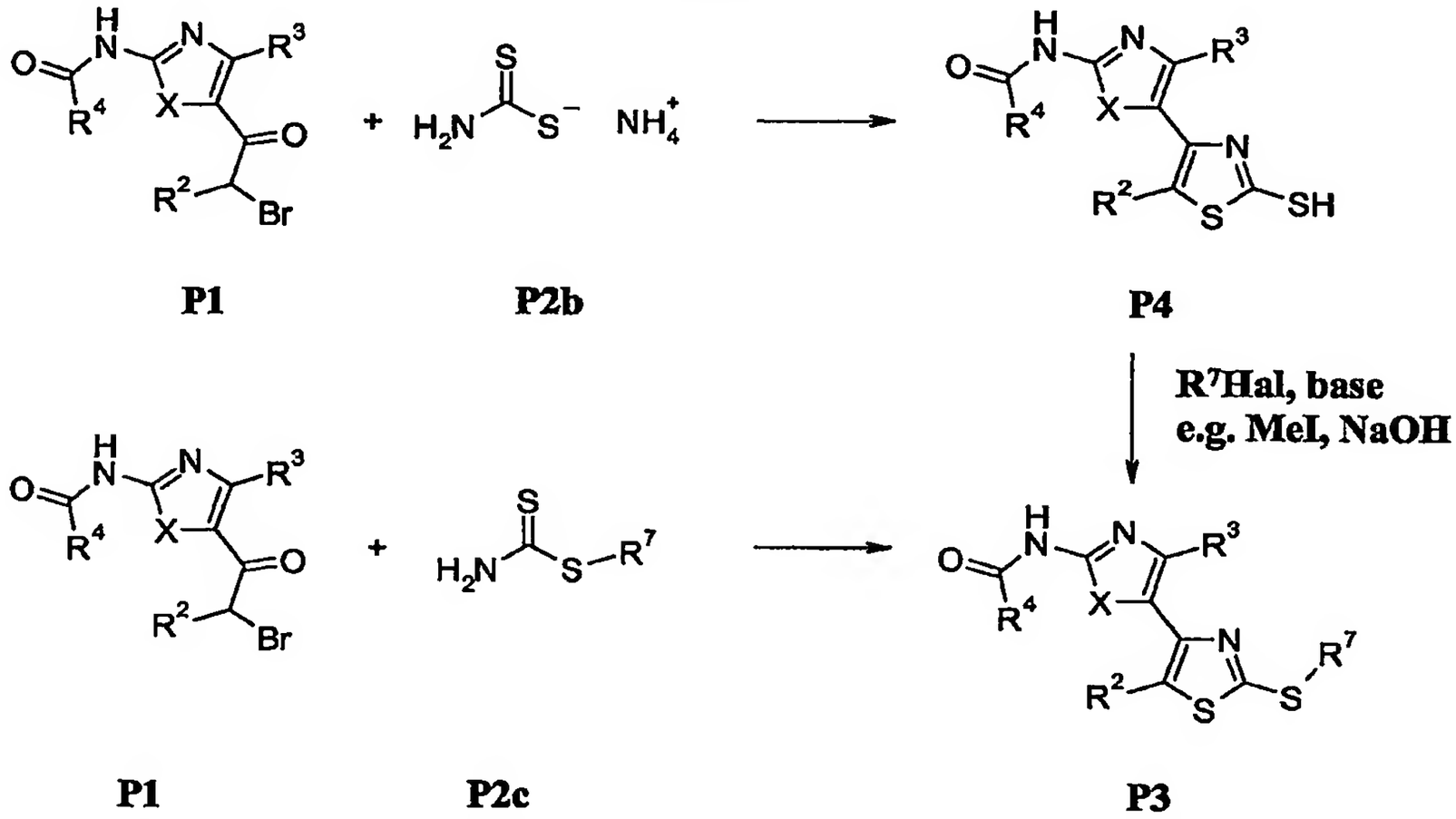
Different chlorination reagents can be used, as for example PCl_5, $POCl_3$ or $SOCl_2$ (*Chanet al., Bioorg. Med. Chem. 1998, 6, 2301-2316*; *Kropf et al., J. Chem. Eng. Data 1988, 33, 537-538*; *El-Maghraby et al., Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry 1981, 20B, 256-257*).

Methods of preparing intermediates of compounds of Formula (I).

Intermediates (P3) and (P4) are obtained by the reaction of approximately equimolar amounts of the α-bromoketone (P1) with Ammonium dithiocarbamate (P2b) or or

dithiocarbamic acid alkyl, alkenyl or alkynyl ester (P2c) respectively as shown below on Scheme 7 below.

Scheme 7



P1 **P2b** **P4**

P1 **P2c** **P3**

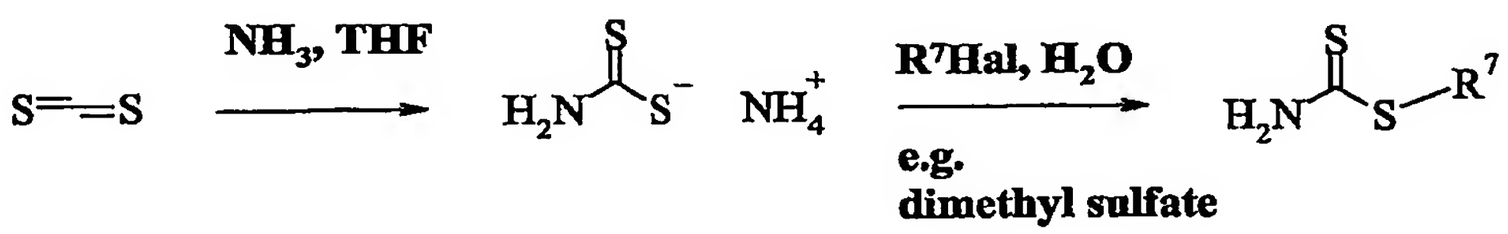
The mixture is stirred as a suspension or solution in a polar solvent, preferably an alcoholic solvent, at a temperature depending on the nature of (P1), (P2b) and (P2c) (*Pattan et al., J. Indian Drugs 2002, 429-433*). The desired bis-thiazole or oxazole-thiazole of formula (P3) or (P4) respectively is isolated by filtration, in case it precipitated out of the reaction mixture upon cooling, or by evaporation of the solvents to obtain the crude product. This crude product can be purified, if desired, e.g. by crystallization or by standard chromatographic methods.

Compound (P3) can be also obtained by direct alkylation of (P4) with R^7Hal in the presence of a base, *e.g.* MeI or any other alkyl, alkenyl or alkynyl halide in the presence of NaOH (*Nair et al., J. Org. Chem. 1975, 40, 1348-1349*).

Ammonium dithiocarbamate (P2b) can be obtained by addition of ammonia to a carbon disulfide solution in a solvent such as THF as shown on Scheme 8 below. It can be further

transformed into (P2c) using R^7Hal, e.g. dimethyl sulfate (*Brandsma et al., Synthesis 1985, 948-949*).

Scheme 8

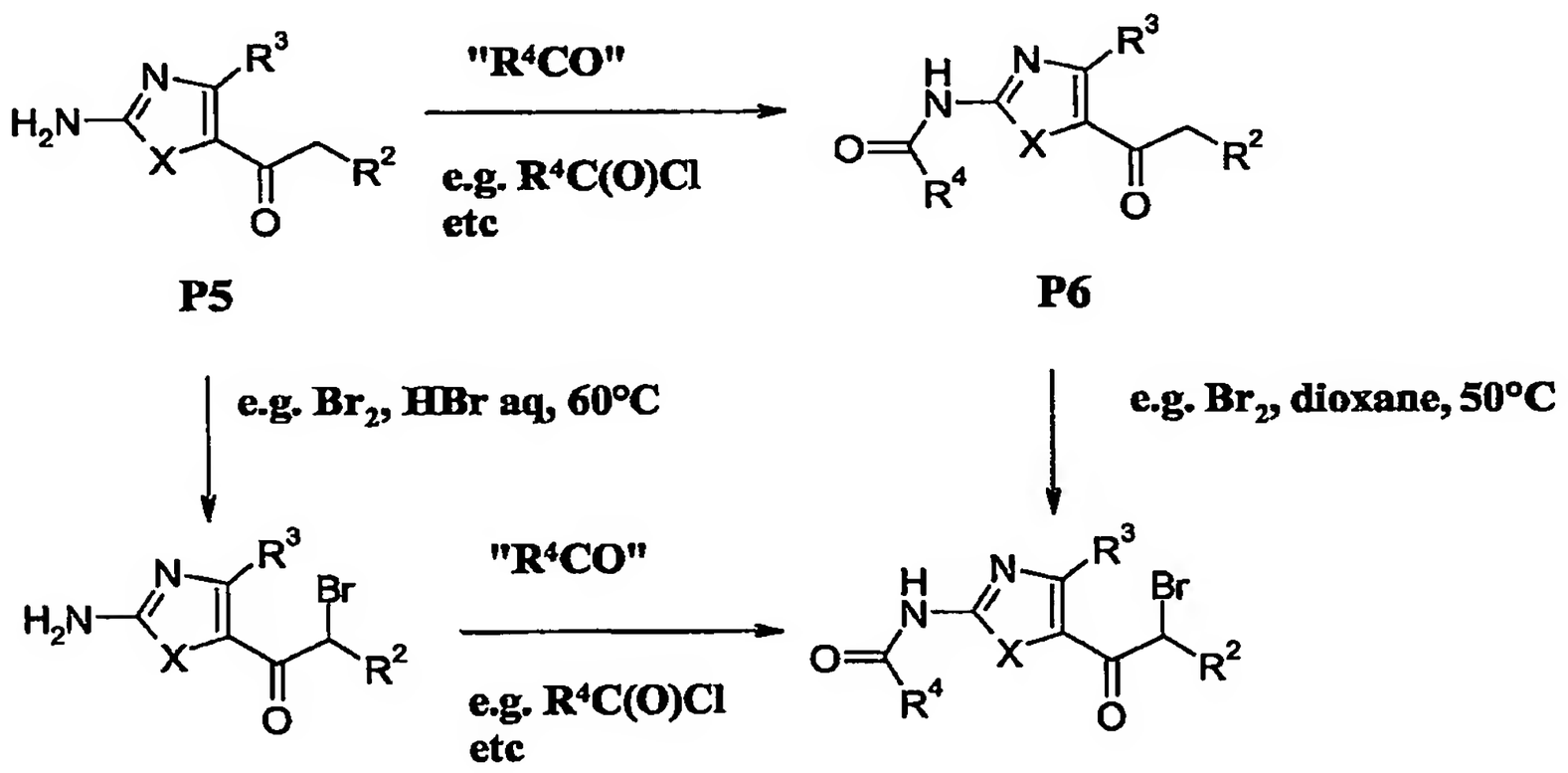


P2b **P2c**

5

α-bromoketone (P1) can be obtained in two steps, from substituted 5-acetyl-2-amino thiazole (P5) as shown on Scheme 9 below.

Scheme 9



P5 **P6**

P1a **P1**

10

Functionalization of the primary amine in (P5) with a group $-C(O)R^4$ as defined above in the description can be performed first, using conditions known to the person skilled in the art to afford (P6).

When $-C(O)R^4$ is an acyl group, the corresponding acyl chloride is added to (P5) in the presence of a base, e.g. pyridine, DIEA, TEA, etc. The corresponding carboxylic acid can be also added in the presence of an activating agent such as DCC, EDC, etc.

A formyl group, $-C(O)R^4 = -C(O)H$, can be introduced by heating (P5) in formic acid or in any alkyl formate, with or without a cosolvent. A substituted urea is formed by addition of an isocyanate, $R^8R^9NC(O)$, to intermediate (P5) in the presence of a base, e.g. DIEA, TEA, etc. The sequential addition of CDI and ammonia to (P5) affords (P6) with $-C(O)R^4 = -C(O)NH_2$.

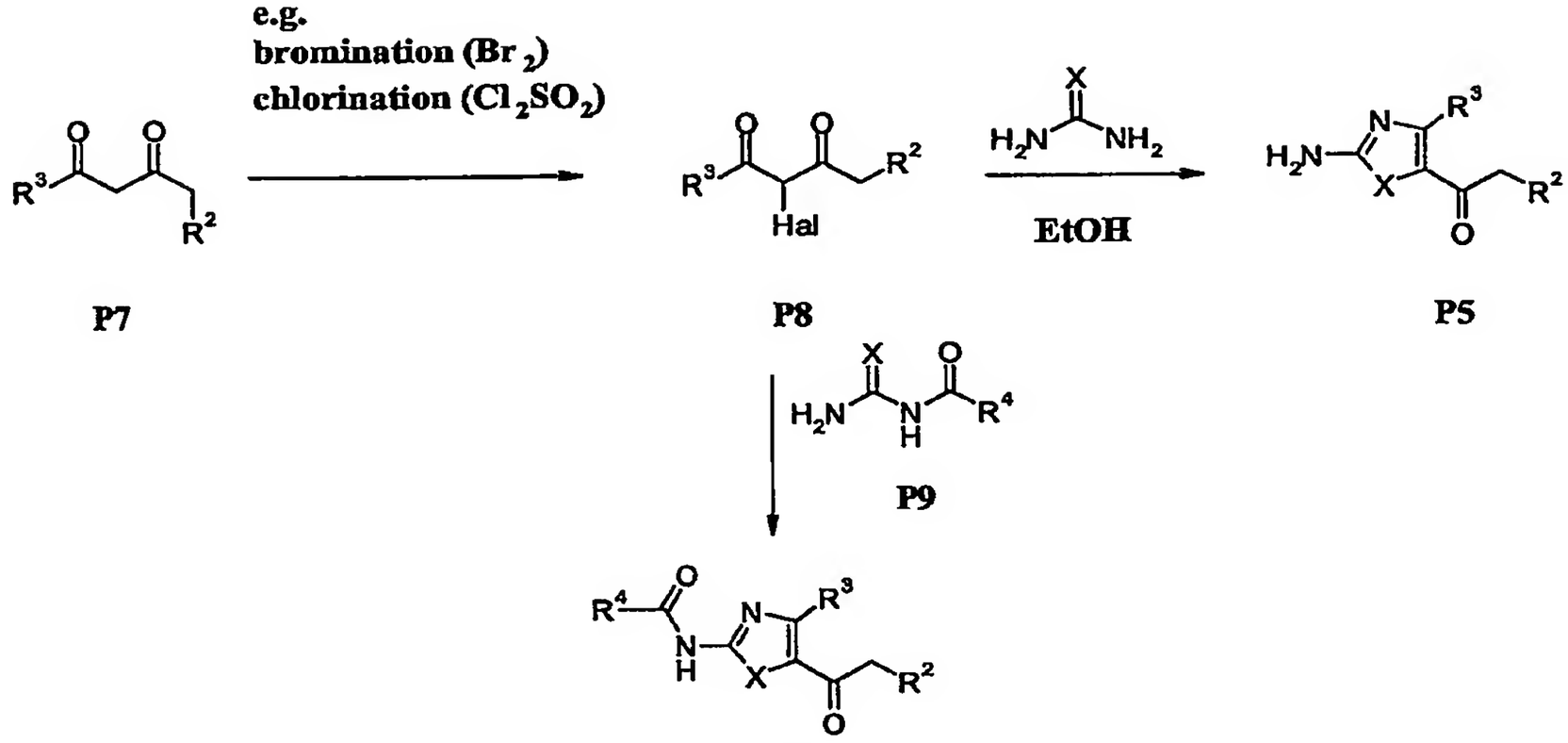
Other $-C(O)R^4$ functionalities can be added to intermediate (P5), to give an intermediate of formula (P6) as defined above in the description, using reaction conditions known to the person skilled in the art. This step is then followed by an α-bromination of the 5-acetyl group to afford intermediate (P1). These two steps can be done in the reverse order, performing first the bromination on intermediate (P5) in the presence of the unprotected primary amine, affording an intermediate (P1a), and then the introduction of $-C(O)R^4$ group as defined above in the description using conditions known to the person skilled in the art to afford an intermediate (P1).

In both synthetic pathway, different bromination agents can be used, such as Br_2 (*Bhatti et al., Indian J. Heterocyclic Chem. 2000, 10, 81-84*), in the optional presence of HBr (*Lipinski et al., J. Med. Chem. 1986, 29, 2154-2163*), NBS (*Sayed et al., Heteroatom Chemistry 1999, 10, 385-390*).

Intermediates according to formula (P5) are either commercially available from various sources or can be obtained by several synthetic approaches, using both solution-phase and solid-phase chemistry protocols (*Kodomari et al., Tetrahedron Lett. 2002, 43, 1717-1720*).

An example of a synthetic approach for obtaining intermediate (P5) is illustrated on Scheme 10 hereinafter.

Scheme 10



A substituted bi-ketone (P7) is halogenated, using for example Br_2 for a bromination or thionyl chloride for a chlorination, affording an intermediate (P8). Intermediate (P8) is then added to a solution of thiourea or urea in a suitable solvent, preferably a polar solvent, e.g. EtOH to lead to an intermediate (P5).

The specific reaction conditions, temperature, time, etc, depend on the nature of X and substituents R^2 and R^3, according to the literature and as it will be detailed below in the examples (*Sayed et al., 1999, above; Dahiya et al., Indian J. Chem. 1986, 25B, 966; Lipinski et al., J. Org. Chem. 1984, 49, 566-570; WO95/01979; EP0117082; JP11209284; Öhler et al., Chem. Ber. 1985, 118, 4099-4130*).

Intermediate (P6) can be directly obtained from the reaction of (P8) with the suitable thiourea or urea (P9), substituted with a $-C(O)R^4$ group as it has been defined above in the description. Thiourea or urea (P9) are either commercially available or obtained by functionalization of urea $H_2NC(O)NH_2$ or thiourea $H_2NC(S)NH_2$ with $-C(O)R^4$, as defined above in the description, using conditions known to the person skilled in the art.

According to a further general process, compounds of Formula (I) can be converted to alter-native compounds of Formula (I), employing suitable interconversion techniques well known by a person skilled in the art.

If the above set of general synthetic methods are not applicable to obtain compounds according to Formula (I) and/or necessary intermediates for the synthesis of compounds of Formula (I), suitable methods of preparation known by a person skilled in the art should be used. In general, the synthesis pathways for any individual compound of Formula (I) will depend on the specific substitutents of each molecule and upon the ready availability of intermediates necessary; again such factors being appreciated by those of ordinary skill in the art. For all the protection and deprotection methods, see Philip J. Kocienski, in "*Protecting Groups*", Georg Thieme Verlag Stuttgart, New York, 1994 and, Theodora W. Greene and Peter G. M. Wuts in "*Protective Groups in Organic Synthesis*", Wiley Interscience, 3rd Edition 1999.

Compounds of this invention can be isolated in association with solvent molecules by crystallization from evaporation of an appropriate solvent. The pharmaceutically acceptable acid addition salts of the compounds of Formula (I), which contain a basic center, may be prepared in a conventional manner. For example, a solution of the free base may be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solution of compound of Formula (I) with a suitable base. Both types of salts may be formed or interconverted using ion-exchange resin techniques.

When employed as pharmaceuticals, the compounds of the present invention are typically administered in the form of a pharmaceutical composition. Hence, pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier, diluent or excipient therefore are also within the scope of the present invention. A

person skilled in the art is aware of a whole variety of such carrier, diluent or excipient compounds suitable to formulate a pharmaceutical composition.

The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous use). Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

Pharmaceutical compositions containing thiazole derivatives of this invention can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of the present invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular and intranasal. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to

produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the thiazole derivative is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As above mentioned, the bisthoiazole derivatives derivatives of Formula (I) in such compositions is typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 5 of *Remington's Pharmaceutical Sciences*, 20th Edition, 2000, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained

release materials can also be found in the incorporated materials in *Remington's Pharmaceutical Sciences*.

In the following the present invention shall be illustrated by means of some examples, which are not construed to be viewed as limiting the scope of the invention.

Examples:

The following intermediate commercially available were used:

5-Acetyl-2-amino-4-methylthiazole and 2,4-pentandione have been used from commercial source.

The commercial amines which have been used as starting material for thiourea synthesis are the following:
4-aminobenzamide, {4-[(4-benzylpiperazin-1-yl)carbonyl]phenyl}amine, morpholine, 1-methylpiperazine, ethyl piperidine-3-carboxylate, 2-piperidin-4-ylethanol, pyrrolidine, pyrrolidin-3-ol, 6-methoxypyridin-3-amine, 6-chloropyridin-3-amine.

Commercial thiourea used in the examples disclosed below are the following:
3-[(aminocarbonothioyl)amino]benzoic acid, 4-[(aminocarbonothioyl)amino]benzoic acid, N-benzylthiourea, N-(2-phenylethyl)thiourea, piperidine-1-carbothioamide, N-allyl thiourea, N-pyridin-3-ylthiourea, N-pyridin-2-ylthiourea, N-(4-methoxyphenyl)thiourea, N-(4-hydroxyphenyl)thiourea, N-(4-nitrophenyl)thiourea, N-(4-cyanophenyl)thiourea, N-(4-chlorophenyl)thiourea, N-(2-chlorophenyl)thiourea, N-(2-methoxyphenyl)thiourea, N-(3-chlorophenyl)thiourea, N-(3-hydroxyphenyl)thiourea, N-(2-morpholin-4-ylethyl)thiourea, N-(2-piperidin-1-ylethyl)thiourea, N-(2-methoxyethyl)thiourea, N-cyclohexylthiourea, N-(3-morpholin-4-ylpropyl)thiourea, N-(tetrahydrofuran-2-ylmethyl)thiourea, N-1-benzofuran-5-ylthiourea.

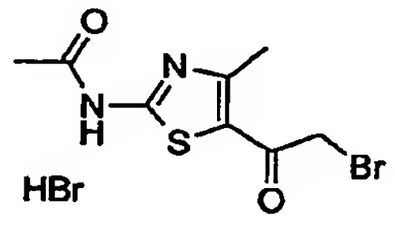
The HPLC, NMR and MS data provided in the examples described below are obtained as followed: HPLC: column Waters Symmetry C8 50 x 4.6 mm, Conditions: MeCN/H_2O, 5 to

100% (8 min), max plot 230-400 nm; Mass spectra: PE-SCIEX API 150 EX (APCI and ESI), LC/MS spectra: Waters ZMD (ES); ^{1}H-NMR: Bruker DPX-300MHz.

The preparative HPLC purifications are performed with HPLC Waters Prep LC 4000 System equipped with columns Prep Nova-Pak®HR C186 µm 60Å, 40x30mm (up to 100mg) or with XTerra® Prep MS C8, 10 µm, 50x300mm (up to 1g). All the purifications are performed with a gradient of MeCN/H_2O 0.09% TFA. The semi-preparative reverse-phase HPLC are performed with the Biotage Parallex Flex System equipped with colums Supelcosil™ ABZ+Plus (25 cm x 21.2 mm, 12 µm); UV detection at 254 nm and 220 nm; flow 20 mL/min (up to 50 mg). TLC Analysis is performed on Merck Precoated 60 F_{254} plates. Purifications by flash chromatography are performed on SiO_2 sup port, using cyclohexane/EtOAc or DCM/MeOH mixtures as eluents.

The microwave chemistry is performed on a single mode microwave reactor Emrys™ Optimiser from Personal Chemistry.

Intermediate 1: Preparation of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl] acetamide, hydrobromide salt (Intermediate (P1) wherein R^2 is H, R^3 and R^4 are methyl and X is S).



Intermediate 1:

Step I: N-(5-acetyl-4-methyl-1,3-thiazol-2-yl)acetamide (Intermediate (P6) wherein R^2 is H, R^3 and R^4 are methyl and X is S)

5-Acetyl-2-amino-4-methylthiazole (P5) (12.35 g, 79 mmol) is suspended in THF/DCM 3:2 mixture (150 mL). The mixture was cooled down to 0°C and pyridine (16 mL) is added, followed by the dropwise addition of acetyl chloride (8.43 mL, 119 mmol, 1.5 eq). The

mixture was stirred 2 hours at 0°C. As the acetylation is complete, the reaction is quenched with addition of water (70 mL) and diluted with EtOAc (100 mL). The two phases are separated and the organic phase is washed with one portion of 10% citric acid solution. Organic layer is dried over $MgSO_4$, filtrated and evaporated. The resulting crude mass is purified by crystallization in EtOAc/Cyclohexane mixture, to obtain N-(5-acetyl-4-methyl-1,3-thiazol-2-yl)acetamide (P6) as a colorless powder (13.13 g, 83.6% yield).

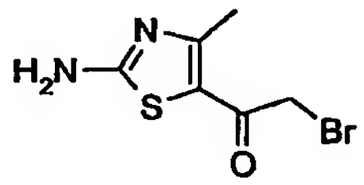
^{1}H NMR (DMSO-d_6) δ: 2.17 (s, 3H), 2.47 (s, 3H), 2.56 (s, 3H), 12.44 (br s, 1H). M^-(ESI): 197.3; M^+(ESI): 199.3. HPLC, Rt: 1.7 min (purity: 99.7%).

Step II: N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt. ***(Intermediate 1)***

A solution of Br_2 (3.36 mL, 65.6 mmol) in 75 mL dioxane is added dropwise to a solution of N-(5-acetyl-4-methyl-1,3-thiazol-2-yl)acetamide (P6), obtained in Step I as described above, (10.40 g, 52.5 mmol) in 200 mL dioxane. The resulting mixture is heated at 50°C for 19 hours. The solution turns from dark red to beige and remains a heterogeneous mixture. By analytical HPLC, only 2.8% of starting material is detected. The suspension is filtered, washed with a 1:2 EtOAc/hexanes mixture (50 mL) and air dried for 15 min, to give **Intermediate 1** as a beige solid (11.2 g, 60%). It is used in bis-thiazol synthesis as HBr salt or as parent, after 5 min treatment with Amberlyst A21 in DCM/MeOH mixture.

^{1}H NMR (DMSO-d_6) δ: 2.04 (s, 3H), 2.44 (s, 3H), 4.52 (s, 2H), 12.44 (br s, 1H). M^-(ESI): 276; M^+(ESI): 278. HPLC, Rt: 2.2 min (purity: 97.4%).

Intermediate 2: Preparation of 1-(2-amino-4-methyl-1,3-thiazol-5-yl)-2-bromo ethanone, hydrobromide salt (Intermediate (P1a) wherein R^2 is H, R^3 is methyl and X is S).

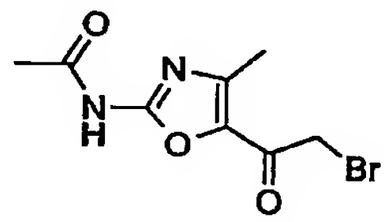


Intermediate 2

5-Acetyl-2-amino-4-methylthiazole (P5) (1.0 g, 6.4 mmol) is suspended in 48% HBr solution in water (20 mL, 6.4 mmol). The mixture is warmed to 60°C and a solution of Br_2 (0.262 mL, 5.12 mmol, 0.8 eq) in dioxane (20 mL) is added dropwise. The mixture is stirred at 60°C for 3 hours. The progression of the reaction is followed by LC/MS. When it is complete, the solvents are evaporated, and the water is removed by azeotropic distillation with toluene. The resulting solid is recrystallized in isopropanol/Et_2O mixture, affording **Intermediate 2** as colorless solid (890 mg, 74% yield).

^{1}H NMR (DMSO-d_6) δ: 2.46 (s, 3H), 4.50 (s, 3H), 6.90 (br s, 1H), 9.18 (br s, 2H). M^-(ESI): 234.1; M^+(ESI): 236.1.

Intermediate 3: Preparation of N-[5-(bromoacetyl)-4-methyl-1,3-oxazol-2-yl] acetamide (Intermediate (P1) wherein R^2 is H, R^3 and R^4 are methyl and X is O).



Intermediate 3

Step I : 3-Bromo-2,4-pentandione (Intermediate (P8) wherein R^2 is H, R^3 is methyl and Hal is Br)

A solution of bromine (55.9 g, 0.35 mol, 18 mL) in CCl_4 (135 mL) is added over 80 min to a bi-phasic solution of 2,4-pentandione (P7) (35 g, 0.35 mol, 36 mL) in 1:1 CCl_4/water mixture (400 mL), keeping the temperature at 3-4°C. 40 min after the addition, both layers are separated and the organic phase is dried over $MgSO_4$. Evaporation under reduced pressure gives 3-bromo-2,4-pentandione (P8) as a slightly yellowish liquid (54.01 g, 86 %).

^{1}H NMR (DMSO-d_6) δ: 2.32 (s, 6H), 5.64 (s, 1H).

Step II : 1-(2-amino-4-methyl-1,3-oxazol-5-yl)ethanone (Intermediate (P5) wherein R^2 is H, R^3 is methyl and X is O).

3-Bromo-2,4-pentandione (P8) (26.66 g, 148.93 mmol) obtained in Step I as described above, is dissolved in acetone (87 mL). This mixture is added to a solution of urea (22.36 g, 372 mmol, 2.5 eq) in water (20 mL). The resulting mixture is heated in order to obtain a clear solution and is distributed into 38 microwave tubes (3 ml each). The vials are heated to 100°C for 1200 s each in the microwave oven. All vials are combined, $NaHCO_3$ sat (100 ml) and EtOAc (100 ml) are added, the aqueous phase is saturated with NaCl and the phases are separated. The aqueous phase is extracted with EtOAc (4 times 100 ml). Combined organic layers are dried over $MgSO_4$, filtrated and evaporated under reduced pressure to give 1-(2-amino-4-methyl-1,3-oxazol-5-yl)ethanone (P5) as an orange solid (12.09 g). It is further recrystallized in MeOH, affording a brownish solid (5.56 g, 27%).

^{1}H NMR (DMSO-d_6) δ: 2.22 (s, 3H), 2.25 (s, 3H), 7.51 (s, 2H).

Step III : N-(5-acetyl-4-methyl-1,3-oxazol-2-yl)acetamide (Intermediate (P6) wherein R^2 is H, R^3 and R^4 are methyl and X is O)

1-(2-amino-4-methyl-1,3-oxazol-5-yl)ethanone (P5) obtained in Step II as described above (12.55 g, 89.58 mmol, 1.00 eq.) is dissolved in pyridine (300 ml). The solution is cooled to 0°C, and acetyl chloride (9.55 ml; 134.37 mmol; 1.50 eq.) is added dropwise at such a rate that the temperature did not exceed 5°C. The mixture is stirred at r.t. overnight. HCl solution (1.0 M, 250 mL) is added and the desired product is extracted with EtOAc (5 times, 100 mL). Combined organic layers are dried over MgSO4, filtrated and evaportated, affording the *N*-(5-acetyl-4-methyl-1,3-oxazol-2-yl)acetamide (P6) as beige/brownish solid (15.18 g, 93%).

^{1}H NMR (DMSO-d_6) δ: 2.12 (s, 3H), 2.34 (s, 3H), 2.35 (s, 3H), 11.64 (s, 1H).

Step IV: N-[5-(bromoacetyl)-4-methyl-1,3-oxazol-2-yl]acetamide ***(Intermediate 3)***

N-(5-acetyl-4-methyl-1,3-oxazol-2-yl)acetamide (P6) obtained in Step III above (13.29 g, 72.95 mmol, 1.00 eq.) is dissolved in glacial acetic acid (250 ml) and 10 drops of hydrobromic acid 62% are added. To the resulting solution, bromine (3.74 ml, 72.95 mmol, 1.00 eq.) is added dropwise and the mixture is stirred at r.t. for 2.5 h. A beige precipitate is formed. It is filtrated off, washed with cyclohexane and dried under reduced pressure to lead to **Intermediate 3** as beige solid (14.89 g, 78 %).

^{1}H NMR (DMSO-d_6) δ: 2.14 (s, 3H), 2.38 (s, 3H), 4.46 (s, 2H), 11.78 (s, 1H). M^-(ESI): 259.8; M^+(ESI): 261.9. HPLC, Rt: 1.3 min (purity: 97.6%).

Thiourea (P2a) preparation: Procedure A

The appropriate amine R^5R^6NH (1 eq) as HCl salt and KSCN (1.5 eq) are heated under reflux in THF (0.5 M). When the reaction is complete, the mixture was diluted with H_2O and extracted with EtOAc (3 portions). Combined organic phases was washed with HCl 1N, brine and dried over Na_2SO_4. After filtration and concentration, the isolated thiourea (P2a) is used in bis-thiazol or oxazole-thiazole synthesis, following general procedure 1 described below.

Thiourea (P2a) preparation: Procedure B

The appropriate amine R^5R^6NH (1 eq) is dissolved in acetone (1 M). This solution is added to a mixture of ethoxycarbonyl isothiocyanate (0.8 eq) in acetone (0.5 M). The reaction progression is followed by LC-MS. When it is complete, aqueous HCl 18% is added and the mixture is extracted with two portions of EtOAc. Combined organic phases are dried over $MgSO_4$, filtrated and evaporated. The products are usually sufficiently pure to be used directly for hydrolysis into the thioureas or eventually purified by flash chromatography.

The resulting N-ethoxycarbonyl thiourea is heated at 100°C in conc. HCl (0.1 M). When the deprotection was complete, the mixture is diluted with water, basified with NH_4OH solution and extracted with EtOAc (3 portions). Combined organic phases are dried over

$MgSO_4$. Filtrated and evaporated isolated thiourea (P2a) is then used in bis-thiazol or oxazole-thiazole synthesis, following general procedure 1 described below.

Thiourea (P2a) preparation: Procedure C

Benzoyl chloride (1.1-1.4 eq.) is added over 5 min to a freshly prepared solution of NH_4SCN (1.1-1.4 eq.) in reagent-grade acetone (0.1 M, endothermic) and the mixture is heated under reflux for about 15 min. Heating is stopped and the appropriate amine R^5R^6NH (1 eq.), either neat or in acetone, is added as rapidly as possible maintaining a vigorous reflux. Following the addition, the mixture is heated under reflux for 15 to 30 min, then poured onto excess cracked ice with vigorous stirring. The resulting solid is collected and liberally washed with H_2O, followed by cold H_2O/MeOH (1:1) or MeOH. The products are usually sufficiently pure to be used directly for hydrolysis into the thioureas or eventually purified by flash chromatography.

The resulting N-benzoylthiourea is added in one portion to a preheated (about 80°C) stirring solution of 5% aqueous NaOH (0.5 M). When the deprotection is complete, the mixture is poored onto ice containing excess aqueous HCl. The pH is adjusted to 8-8.5 with NH_4OH. The desired thiourea is filtrated and washed with NH_4OH and water, or extracted with EtOAc (3 portions) and dried over $MgSO_4$. Isolated thiourea (P2a) is then used in the bis-thiazol or oxazole-thiazole synthesis, following general procedure 1 described below.

Thiourea (P2a) preparation: Procedure D

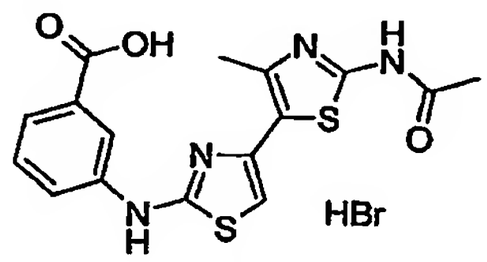
The appropriate amine R^5R^6NH (1 eq.) is added to a 1:1 chloroform/water mixture (0.1 M). Saturated $NaHCO_3$ solution in water (3 eq) followed by thiophosgene (1.1 eq.) are added dropwise at 0°C. The bi-phasic mixture is stirred overnight at r.t. The reaction progression is followed by TLC. After completion, the organic phase is separated, washed with water and dried over $MgSO_4$. A saturated solution of ammonia in ethanol (1 vol) is added to the chloroform solution, and stirred overnight at r.t. The reaction mixture is concentrated affording the expected thiourea, which is kept as crude product or recrystallized in a

suitable solvent. Isolated thiourea is used in the bis-thiazole or oxazole-thiazole synthesis, following general procedure 1 described below.

Bis-Thiazole or Oxazole-Thiazole Synthesis: General procedure 1

Intermediate P1 or P1a is dissolved in EtOH (0.5 M) and the appropriate thiourea is added (1 eq). When P1 or P1a is used as salt, TEA (3 eq) is added before the addition of the thiourea. The mixture is stirred for 1 to 24 h at temperatures ranging from –20°C to reflux. When the reaction is complete, TEA (2-3 eq) is added. The desired product (Ia) or (Ib) is isolated as indicated in the examples below.

Example 1: 3-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}benzoic acid, hydrobromide salt

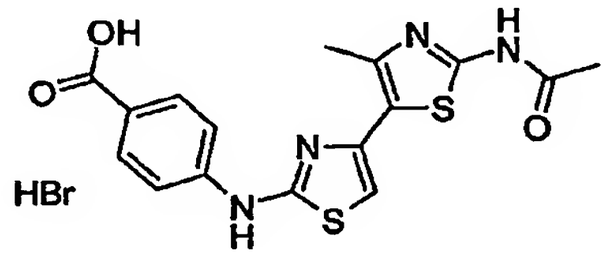


(1)

According to the general procedure 1, 3-[(aminocarbonothioyl)amino]benzoic acid (Aldrich) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at r.t. for 30 min. The desired product is filtrated off the reaction mixture and washed with cold EtOH. Compound **(1)** is isolated as a kaki solid (68%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.13 (s, 3H), 2.51 (s, 3H), 6.93 (s, 1H), 7.44 (m, 1H), 7.49 (m, 1H), 7.92 (m, 1H), 8.25 (m, 1H), 10.49 (s, 1H), 11.83 (br s, 1H). M^-(ESI): 373; M^+(ESI): 375. HPLC, Rt: 2.6 min (purity: 92.8 %).

Example 2: 4-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}benzoic acid, hydrobromide salt



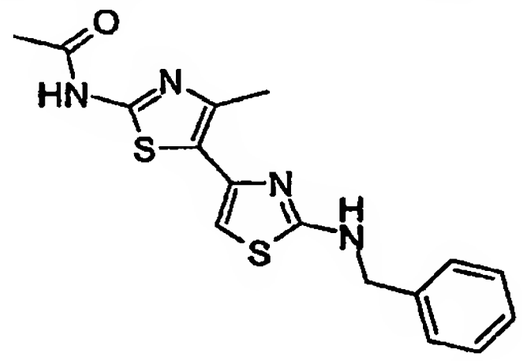
(2)

According to the general procedure 1, 4-[(aminocarbonothioyl)amino]benzoic acid (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide (**Intermediate 1**) in EtOH.

The mixture is stirred at r.t. for 30 min. The desired product is filtrated off the reaction mixture and washed with cold EtOH. Compound **(2)** is isolated as a white solid (67%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.13 (s, 3H), 2.49 (m, 3H), 7.00 (s, 1H), 7.73 (d, J=9 Hz, 2H), 7.90 (d, J=9 Hz, 2H), 10.71 (s, 1H), 12.07 (s, 1H). M^-(ESI): 373; M^+(ESI): 375. HPLC, Rt: 3 min (purity: 95 %).

Example 3: N-[2-(benzylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide

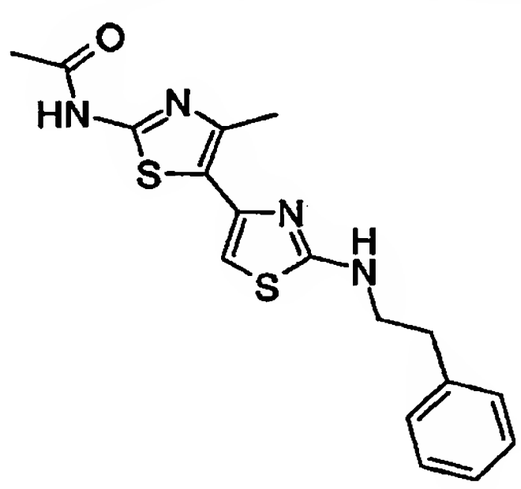


(3)

According to the general procedure 1, N-benzylthiourea (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide (**Intermediate 1**) in EtOH. The mixture is stirred at reflux for 1.5 h. TEA (2 eq) is then added. The solvents are evaporated and the desired product is purified by flash chromatography. Compound **(3)** is isolated as a light yellow solid (34%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.27 (s, 3H), 2.56 (s, 3H), 4.61 (m, 2H), 6.78 (s, 1H), 7.49 (m, 5H), 8.40 (m, 1H), 12.14 (s, 1H). M^-(ESI): 343; M^+(ESI): 345. HPLC, Rt: 2.79 min (purity: 99.6 %).

Example 4: N-{4-methyl-2-[(2-phenylethyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide

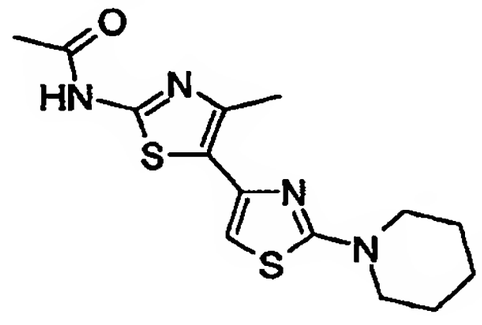


(4)

According to the general procedure 1, N-(2-phenylethyl)thiourea (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at reflux for 1.5 h. TEA (2 eq) is then added. The solvents are evaporated and the desired product is purified by flash chromatography. Compound **(4)** was isolated is a light yellow solid (74%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.93 (s, 3H), 2.25 (s, 3H), 2.70 (t, J=7.5 Hz, 2H), 3.26 (m, 2H), 6.43 (s, 1H), 7.07 (m, 5H), 7.64 (m, 1H), 11.79 (s, 1H). M^-(ESI): 357; M^+(ESI): 359. HPLC, Rt: 2.79 min (purity: 93.3 %).

Example 5: N-(4-methyl-2-piperidin-1-yl-4,5-bi-1,3-thiazol-2-yl)acetamide

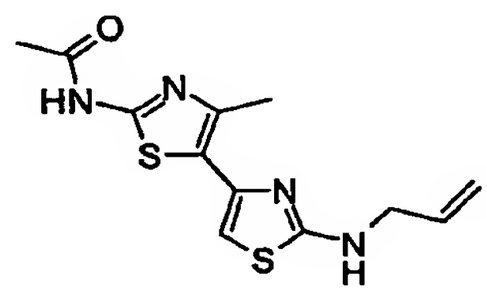


(5)

According to the general procedure 1, piperidine-1-carbothioamide (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at reflux for 1.5 h. TEA (2 eq) is then added. The solvents are evaporated and the desired product is purified by flash chromatography. Compound **(5)** is isolated as a colorless solid (82%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.46 (m, 6H), 1.98 (s, 3H), 2.29 (s, 3H), 3.29 (m, 4H), 6.64 (s, 1H), 11.86 (s, 1H). M^-(ESI): 321; M^+(ESI): 323. HPLC, Rt: 2.73 min (purity: 95.2 %).

Example 6: N-[2-(allylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide

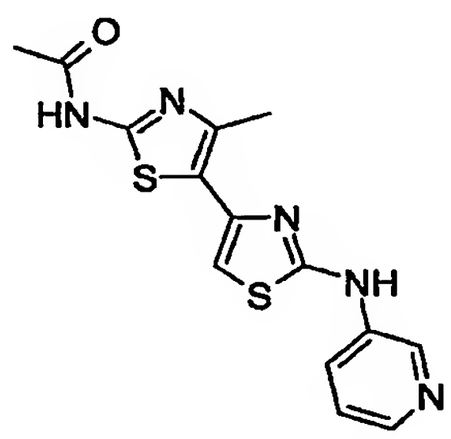


(6)

According to the general procedure 1, N-allylthiourea (Fluka) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at reflux for 1.5 h. TEA (2 eq) is then added. The solvents are evaporated and the desired product is purified by flash chromatography. Compound **(6)** is isolated as a light green solid (65%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.14 (s, 3H), 2.44 (s, 3H), 3.90 (m, 2H), 5.13 (dd, J=3 Hz, J= 12 Hz, 1H), 5.28 (dd, J=3 Hz, J=18 Hz, 1H), 5.94 (m, 1H), 6.65 (s, 1H), 7.89 (m, 1H), 11.99 (s, 1H). M^-(ESI): 293; M^+(ESI): 295. HPLC, Rt: 1.99 min (purity: 98.7 %).

Example 7: N-[4-methyl-2-(pyridin-3-ylamino)-4,5-bi-1,3-thiazol-2-yl]acetamid

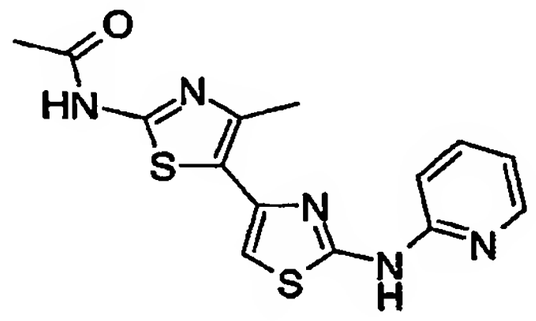


(7)

According to the general procedure 1, N-pyridin-3-ylthiourea (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at reflux for 1 h. TEA (2 eq) is then added. After addition of water, the desired product is filtrated off and washed with water. Compound **(7)** is isolated as a yellow orange solid (91%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.18 (s, 3H), 2.53 (m, 3H), 7.01 (s, 1H), 7.41 (m, 1H), 8.17 (m, 1H), 8.22 (m, 1H), 8.89 (d, J=3 Hz, 1H), 10.57 (s, 1H), 12.11 (s, 1H). M^-(ESI): 330; M^+(ESI): 332. HPLC, Rt: 1.97 min (purity: 98 %).

Example 8: N-[4-methyl-2-(pyridin-2-ylamino)-4,5-bi-1,3-thiazol-2-yl]acetamide

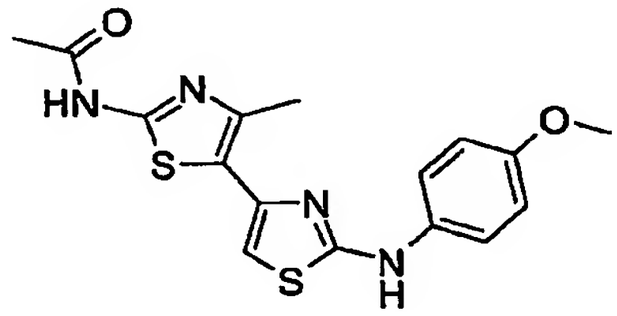


(8)

According to the general procedure 1, N-pyridin-2-ylthiourea (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at reflux for 2 h. TEA (2 eq) is then added. The solvents are evaporated and the desired product is purified by flash chromatography. Compound **(8)** is isolated as a beige yellow solid (51%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.17 (s, 3H), 2.51 (s, 3H), 6.98 (m, 1H), 7.05 (s, 1H), 7.12 (m, 1H), 7.75 (m, 1H), 8.35 (m, 1H), 11.49 (s, 1H), 12.07 (br s, 1H). M$^-$(ESI): 330; M$^+$(ESI): 332. HPLC, Rt: 2.07 min (purity: 98.2 %).

Example 9: N-{2-[(4-methoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl} acetamide



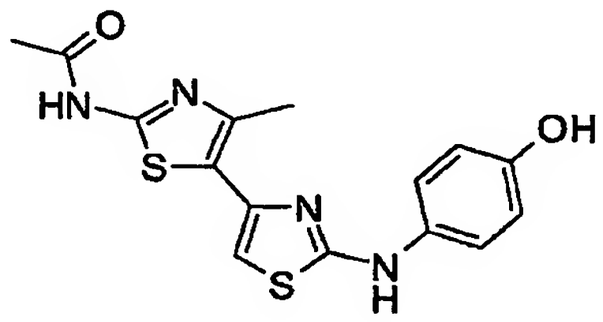
(9)

According to the general procedure 1, N-(4-methoxyphenyl)thiourea (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at reflux for 2 h. TEA (2 eq) is then added. The solvents are

evaporated and the desired product is purified by flash chromatography. Compound **(9)** is isolated as a brown solid (60%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.25 (s, 3H), 2.54 (s, 3H), 3.82 (s, 3H), 6.68 (s, 1H), 6.94 (m, 2H), 7.57 (m, 2H). M^-(ESI): 359; M^+(ESI): 361. HPLC, Rt: 3.29 min (purity: 96.3 %).

Example 10: N-{2-[(4-hydroxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl} acetamide

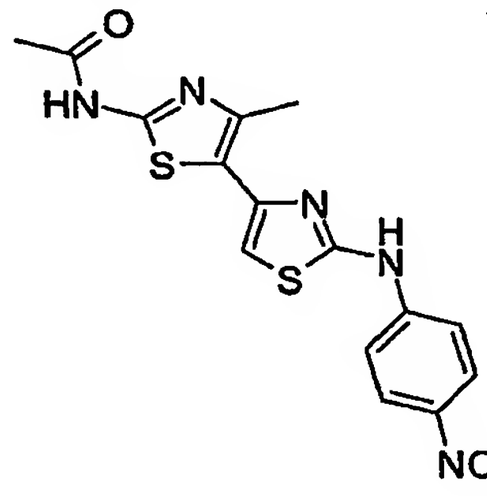


(10)

According to the general procedure 1, N-(4-hydroxyphenyl)thiourea (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture was stirred at reflux for 2 h. TEA (2 eq) is then added. The solvents are evaporated and the desired product is purified by flash chromatography. Compound **(10)** is isolated as a light pink solid (50%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.17 (s, 3H), 2.50 (s, 3H), 6.79 (m, 3H), 7.43 (m, 2H), 9.19 (s, 1H), 9.98 (s, 1H), 12.07 (s, 1H). M^-(ESI): 345; M^+(ESI): 347. HPLC, Rt: 2.52 min (purity: 99 %).

Example 11: N-{4-methyl-2-[(4-nitrophenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide

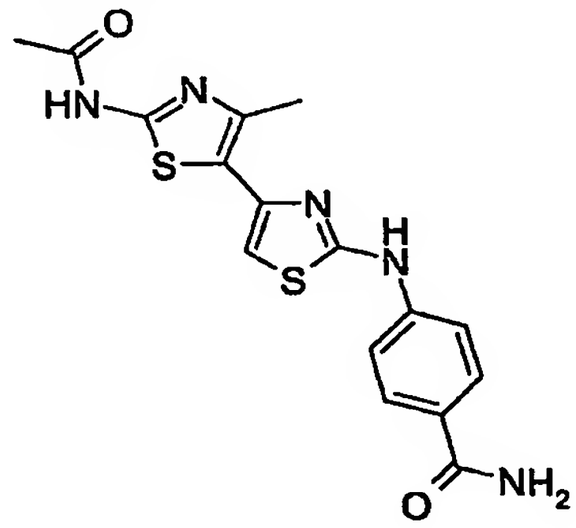


(11)

According to the general procedure 1, N-(4-nitrophenyl)thiourea (Aldrich) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at reflux for 20 h. TEA (2 eq) is then added. The solvents are evaporated and the desired product is purified by flash chromatography. Compound **(11)** is isolated as an orange solid (40%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.13 (s, 3H), 2.49 (s, 3H), 7.10 (s, 1H), 7.83 (m, 2H), 8.23 (m, 2H), 11.10 (s, 1H), 12.09 (s, 1H). M^-(ESI): 374; M^+(ESI): 376. HPLC, Rt: 3.69 min (purity: 100 %).

Example 12: 4-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}benzamide

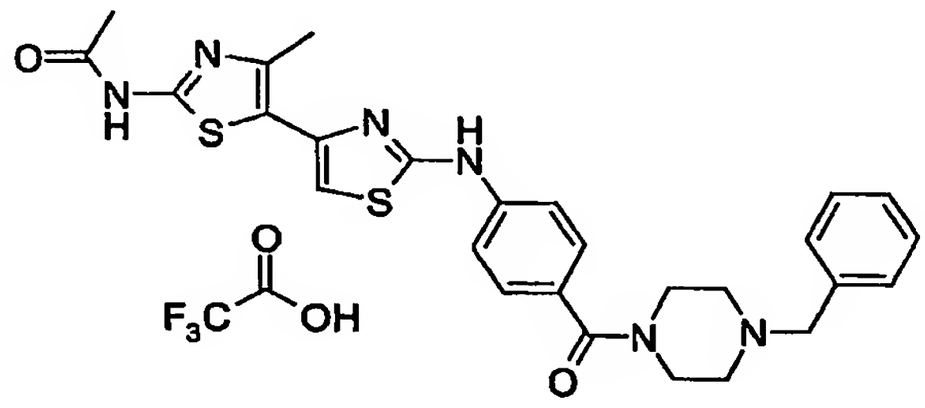


(12)

According to the general procedure 1, 4-[(aminocarbonothioyl)amino]benzamide (obtained from 4-aminobenzamide from Aldrich following procedure C) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at reflux for 1.5 h. TEA (2 eq) is then added. After addition of water, the desired product is filtrated off and washed with water. It is then purified by flash chromatography. Compound **(12)** is isolated as a light beige solid (29%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.14 (s, 3H), 2.49 (s, 3H), 6.97 (s, 1H), 7.16 (br s, 1H), 7.70 (m, 2H), 7.85 (m, 3H), 10.60 (s, 1H), 12.07 (s, 1H). M^-(ESI): 372; M^+(ESI): 374. HPLC, Rt: 2.73 min (purity: 99.5 %).

Example 13: N-[2-({4-[(4-benzylpiperazin-1-yl)carbonyl]phenyl}amino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide, trifluoroacetate salt

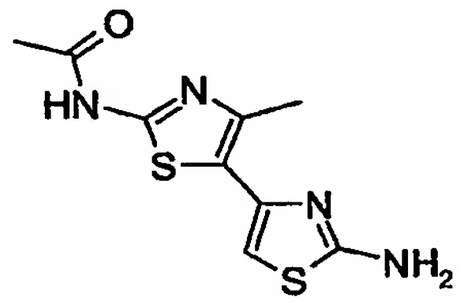


(13)

According to the general procedure 1, N-{4-[(4-benzylpiperazin-1-yl)carbonyl] phenyl}thiourea (obtained from commercial {4-[(4-benzylpiperazin-1-yl)carbonyl] phenyl}amine following procedure C) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at reflux for 2 h. TEA (2 eq) is then added. The solvents are evaporated and the desired product is purified by preparative HPLC. Compound **(13)** is isolated as a beige solid (42%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.13 (s, 3H), 2.49 (s, 3H), 3.25 (m, 6H), 3.88 (m, 2H), 4.36 (m, 2H), 6.98 (s, 1H), 7.47 (m, 7H), 7.73 (m, 2H), 9.90 (br s, 1H), 10.60 (s, 1H), 12.08 (s, 1H). M^-(ESI): 531; M^+(ESI): 533. HPLC, Rt: 2.76 min (purity: 99.9 %).

Example 14: N-(2-amino-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide

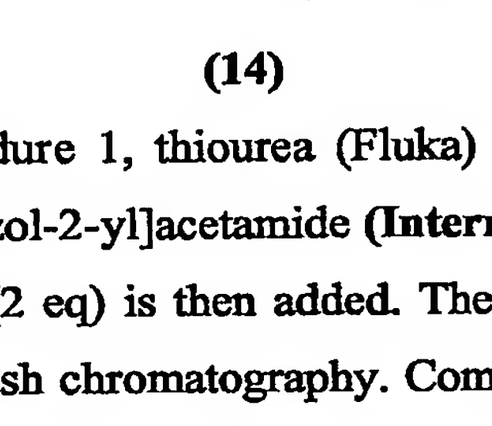


(14)

According to the general procedure 1, thiourea (Fluka) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at r.t. for 1.5 h. TEA (2 eq) is then added. The solvents are evaporated and the desired product is purified by flash chromatography. Compound **(14)** is isolated as a beige solid (81%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.17 (s, 3H), 2.47 (s, 3H), 6.62 (s, 1H), 7.18 (br s, 2H), 12.02 (s, 1H). M^-(ESI): 253; M^+(ESI): 255. HPLC, Rt: 1.21 min (purity: 99.9 %).

Example 15: N-(2-anilino-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide



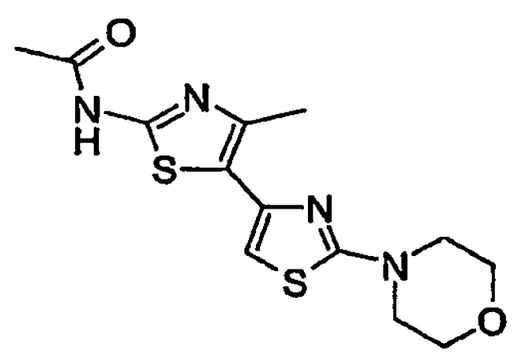
(15)

According to the general procedure 1, N-phenylthiourea (Aldrich) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 1 h. TEA (3 eq) is then

added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. Compound **(15)** is isolated as a brown green solid (quantitative).

^1H NMR (DMSO-d_6, 300 MHz) δ 2.13 (s, 3H), 2.48 (s, 3H), 6.68 (s, 1H), 6.96 (m, 1H), 7.32 (m, 2H), 7.63 (m, 2H), 10.29 (s, 1H), 12.00 (s, 1H). M^-(ESI): 329; M^+(ESI): 331. HPLC, Rt: 3.45 min (purity: 96.6 %).

Example 16: N-(4-methyl-2-morpholin-4-yl-4,5-bi-1,3-thiazol-2-yl)acetamide

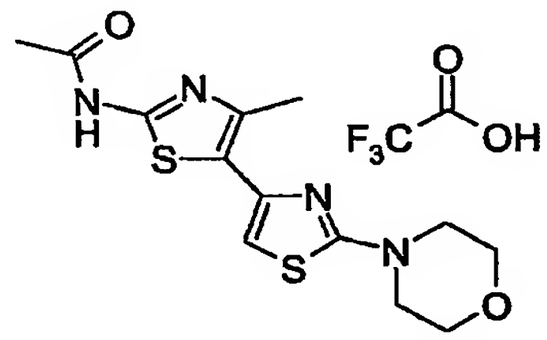


(16)

According to the general procedure 1, morpholine-4-carbothioamide (obtained from morpholine from Fluka following procedure B) is added to a solution of of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 1 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. It is then purified by flash chromatography. Compound **(16)** is isolated as a light beige solid (74%).

^1H NMR (DMSO-d_6, 300 MHz) δ 2.14 (s, 3H), 2.46 (s, 3H), 3.42 (m, 4H), 3.74 (m, 4H), 6.89 (s, 1H), 12.03 (s, 1H). M^-(ESI): 323; M^+(ESI): 325. HPLC, Rt: 2.5 min (purity: 99.5 %).

Example 17: N-[4-methyl-2-(4-methylpiperazin-1-yl)-4,5-bi-1,3-thiazol-2-yl]acetamide, trifluoroacetate salt

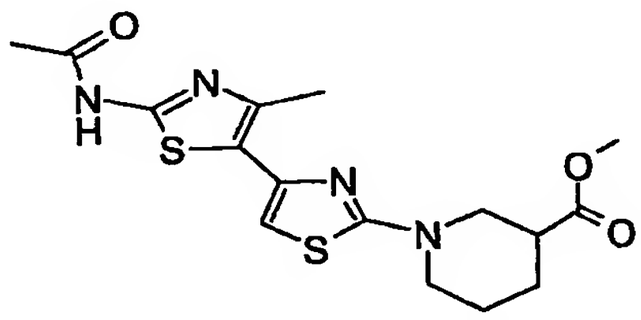


(17)

According to the general procedure 1, 4-methylpiperazine-1-carbothioamide (obtained from 1-methylpiperazine from Fluka following procedure B) is added to a solution of of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 2 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. It is then purified by preparative HPLC. Compound **(17)** isolated as a green oil (67%).

^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 2.58 (s, 3H), 2.86 (s, 3H), 3.10 (m, 2H), 3.83 (m, 6H), 6.71 (s, 1H), 14.92 (br s, 1H). M^-(ESI): 336; M^+(ESI): 338. HPLC, Rt: 1.71 min (purity: 93 %).

Example 18: methyl 1-[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]piperidine-3-carboxylate

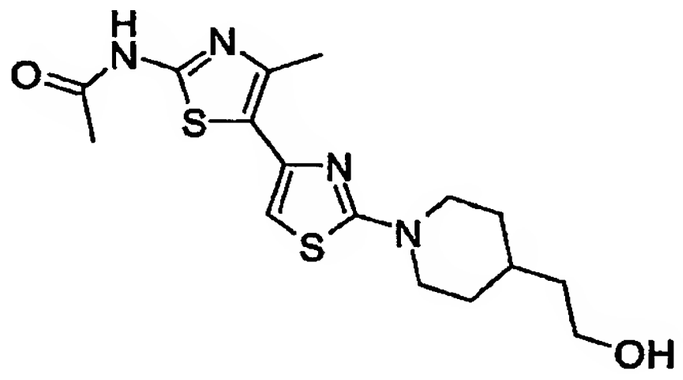


(18)

According to the general procedure 1, ethyl 1-(aminocarbonothioyl)piperidine-3-carboxylate (obtained from ethyl piperidine-3-carboxylate from Fluka following procedure B) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 1 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. It is then purified by flash chromatography. Compound **(18)** is isolated as a light yellow solid (61%).

^1H NMR (DMSO-d_6, 300 MHz) δ 1.72 (m, 3H), 2.01 (m, 1H), 2.16 (s, 3H), 2.47 (s, 3H), 2.73 (m, 1H), 3.22 (m, 1H), 3.37 (m, 1H), 3.68 (s, 3H), 3.71 (m, 1H), 4.00 (m, 1H), 6.86 (s, 1H), 12.05 (s, 1H). M^-(ESI): 379; M^+(ESI): 381. HPLC, Rt: 3.11 min (purity: 90.8 %).

Example 19: N-{2-[4-(2-hydroxyethyl)piperidin-1-yl]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide



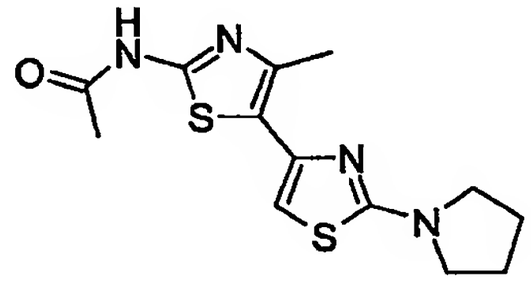
(19)

According to the general procedure 1, 4-(2-hydroxyethyl)piperidine-1-carbothioamide (obtained from 2-piperidin-4-ylethanol from Aldrich following procedure B) is added to a solution of of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 1 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. It is then purified by flash chromatography. Compound **(19)** is isolated as a beige solid (48%).

^1H NMR (DMSO-d_6, 300 MHz) δ 1.25 (m, 2H), 1.44 (m, 2H), 1.68 (m, 1H), 1.79 (m, 2H), 2.16 (s, 3H), 2.47 (s, 3H), 3.05 (m, 2H), 3.51 (m, 2H), 3.92 (m, 2H), 4.43 (t, J=6 Hz, 1H),

6.82 (s, 1H), 12.04 (s, 1H). M^-(ESI): 365; M^+(ESI): 367. HPLC, Rt: 2.25 min (purity: 95.9 %).

Example 20: N-(4-methyl-2-pyrrolidin-1-yl-4,5-bi-1,3-thiazol-2-yl)acetamide

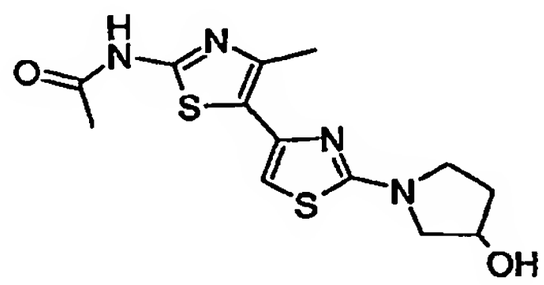


(20)

According to the general procedure 1, pyrrolidine-1-carbothioamide (obtained from pyrrolidine from Fluka following procedure B) is added to a solution of of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 1 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. It is then purified by flash chromatography. Compound **(20)** is isolated as a light yellow solid (50%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.00 (m, 4H), 2.14 (s, 3H), 2.45 (s, 3H), 3.41 (m, 4H), 6.72 (s, 1H), 12.00 (s, 1H). M^-(ESI): 307; M^+(ESI): 309. HPLC, Rt: 1.83 min (purity: 98.8 %).

Example 21: N-[2-(3-hydroxypyrrolidin-1-yl)-4-methyl-4,5-bi-1,3-thiazol-2-yl] acetamide

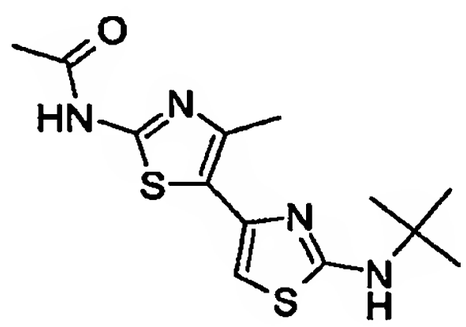


(21)

According to the general procedure 1, 3-hydroxypyrrolidine-1-carbothioamide (obtained from pyrrolidin-3-ol from Aldrich following procedure B) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 1 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. It is then purified by flash chromatography. Compound **(21)** is isolated as a light beige solid (54%).

^1H NMR (DMSO-d_6, 300 MHz) δ 1.85-1.96 (m, 1H), 2.0-2.14 (m, 1H), 2.11 (s, 3H), 2.42 (s, 3H), 3.27 (m, 1H), 3.41-3.56 (m, 3H), 4.40 (br s, 1H), 5.05 (d, J=3 Hz, 1H), 6.69 (s, 1H), 11.97 (br s, 1H). M^-(ESI): 323.2; M^+(ESI): 325.2. HPLC, Rt: 1.4 min (purity: 98.4 %).

Example 22: N-[2-(tert-butylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide

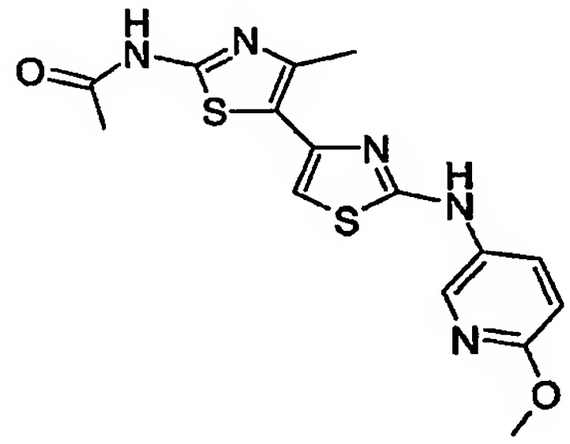


(22)

According to the general procedure 1, N-(tert-butyl)thiourea (Lancaster) is added to a solution of of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at r.t. for 1.5 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. Compound **(22)** is isolated as a dark yellow solid (quantitative).

^1H NMR (DMSO-d_6, 300 MHz) δ 1.38 (s, 9H), 2.10 (s, 3H), 2.42 (s, 3H), 6.55 (s, 1H), 7.43 (s, 1H), 11.70 (s, 1H). M^-(ESI): 309.3; M^+(ESI): 311.3. HPLC, Rt: 2.5 min (purity: 96.7 %).

Example 23: N-{2-[(6-methoxypyridin-3-yl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide

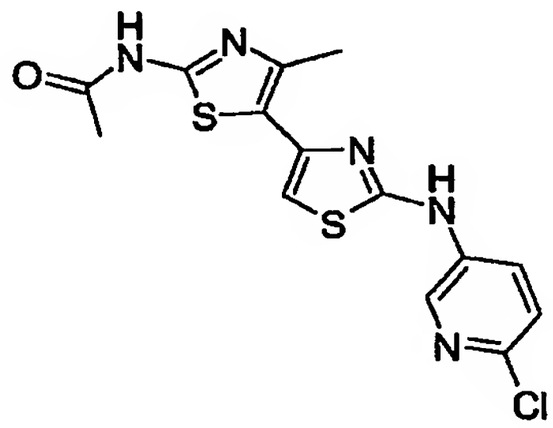


(23)

According to the general procedure 1, N-(6-methoxypyridin-3-yl)thiourea (obtained from 6-methoxypyridin-3-amine from Aldrich following procedure C) is added to a solution of of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 2h. TEA (3 eq) is then added. After addition of water, the desired product is filtrated off and washed with water. Compound **(23)** is isolated as a brown-beige solid (73%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.15 (s, 3H), 2.49 (s, 3H), 3.85 (s, 3H), 6.86 (d, J=9 Hz, 1H), 6.89 (s, 1H), 7.91 (dd, J=3, 9 Hz, 1H), 8.63 (d, J=3 Hz, 1H), 10.24 (s, 1H), 12.06 (s, 1H). M^-(ESI): 360.3; M^+(ESI): 362.2. HPLC, Rt: 2.6 min (purity: 97.6 %).

Example 24: N-{2-[(6-chloropyridin-3-yl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide

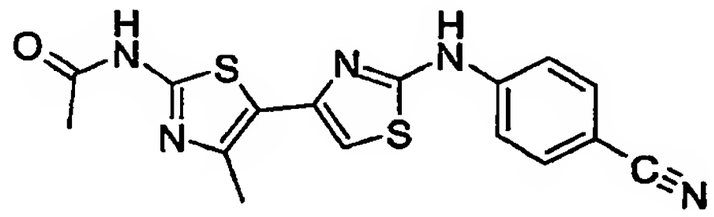


(24)

According to the general procedure 1, N-(6-chloropyridin-3-yl)thiourea (obtained from 6-chloropyridin-3-amine from Aldrich following procedure C) is added to a solution of of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 2 h. TEA (3 eq) is then added. After addition of water, the desired product is filtrated off and washed with water. Compound **(24)** is isolated as a light beige solid (72%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.16 (s, 3H), 2.50 (s, 3H), 7.02 (s, 1H), 7.51 (d, J=9 Hz, 1H), 8.13 (dd, J=3, 9 Hz, 1H), 8.79 (d, J=3 Hz, 1H), 10.70 (s, 1H), 12.09 (s, 1H). M^-(ESI): 364; M^+(ESI): 366. HPLC, Rt: 3.3 min (purity: 98.7 %).

Example 25: N-{2-[(4-cyanophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide

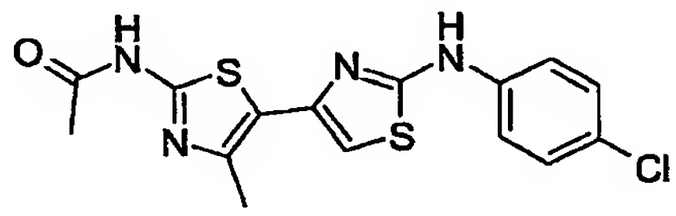


(25)

According to the general procedure 1, N-(4-cyanophenyl)thiourea (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 2 h. TEA (3 eq) is then added. After addition of water, the desired product is filtrated off and washed with water. Compound **(25)** is isolated as a beige solid (72%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.13 (s, 3H), 2.50 (s, 3H), 7.05 (s, 1H), 7.78 (m, 4H), 10.85 (s, 1H), 11.95 (s, 1H). M^-(ESI): 354.3; M^+(ESI): 356.3. HPLC, Rt: 3.5 min (purity: 99.5 %).

Example 26: N-{2-[(4-chlorophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl} acetamide

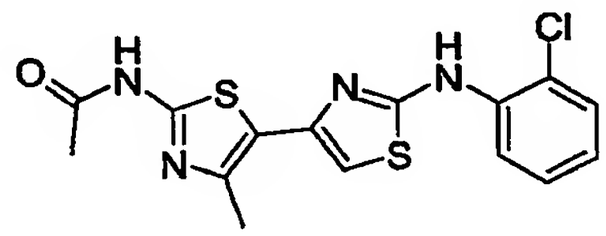


(26)

According to the general procedure 1, N-(4-chlorophenyl)thiourea (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 2 h. TEA (3 eq) is then added. After addition of water, the desired product is filtrated off and washed with water. Compound **(26)** is isolated as a beige solid (47%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.13 (s, 3H), 2.47 (s, 3H), 6.92 (s, 1H), 7.37 (m, J=9 Hz, 2H), 7.66 (m, J=9 Hz, 2H), 10.43 (s, 1H), 11.85 (s, 1H). M^-(ESI): 363; M^+(ESI): 365. HPLC, Rt: 3.9 min (purity: 99.9 %).

Example 27: N-{2-[(2-chlorophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl} acetamide

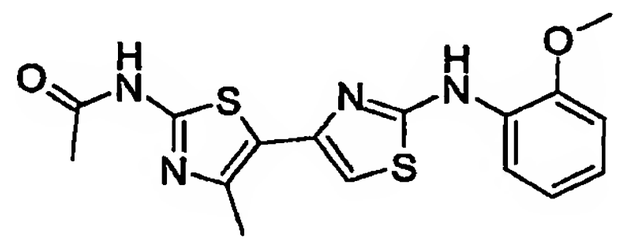


(27)

According to the general procedure 1, N-(2-chlorophenyl)thiourea (Lancaster) is added to a solution of of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 2 h. TEA (3 eq) is then added. After addition of water, the desired product is filtrated off and washed with water. Compound **(27)** is isolated as a brown solid (59%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.12 (s, 3H), 2.45 (s, 3H), 6.93 (s, 1H), 7.06 (m, 1H), 7.34 (m, 1H), 7.48 (m, 1H), 8.30 (m, 1H), 9.73 (s, 1H), 12.10 (s, 1H). M^-(ESI): 363; M^+(ESI): 365. HPLC, Rt: 3.8 min (purity: 97.7 %).

Example 28: N-{2-[(2-methoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl} acetamide

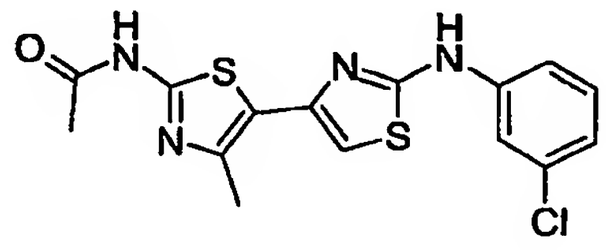


(28)

According to the general procedure 1, N-(2-methoxyphenyl)thiourea (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 2 h. TEA (3 eq) is then added. After addition of water, the desired product is filtrated off and washed with water. Compound **(28)** is isolated as a white solid (69%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.12 (s, 3H), 2.46 (s, 3H), 3.85 (s, 3H), 6.84 (s, 1H), 6.91-7.05 (m, 3H), 8.33 (m, 1H), 9.59 (s, 1H), 11.85 (s, 1H). M^-(ESI): 359; M^+(ESI): 361. HPLC, Rt: 3.5 min (purity: 100 %).

Example 29: N-{2-[(3-chlorophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl} acetamide



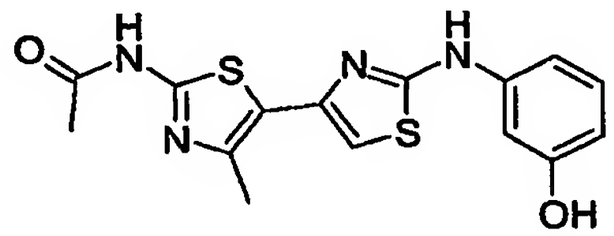
(29)

According to the general procedure 1, N-(3-chlorophenyl)thiourea (Lancaster) is added to a solution of of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt

(Intermediate 1) and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 2 h. TEA (3 eq) is then added. After addition of water, the desired product is filtrated off and washed with water. Compound **(29)** is isolated as a beige solid (81%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.13 (s, 3H), 2.50 (s, 3H), 6.95 (s, 1H), 7.00 (m, 1H), 7.33 (m, 1H), 7.40 (m, 1H), 8.00 (s, 1H), 10.52 (s, 1H), 12.10 (s, 1H). M^-(ESI): 363; M^+(ESI): 365. HPLC, Rt: 3.9 min (purity: 99.8 %).

Example 30: N-{2-[(3-hydroxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl} acetamide

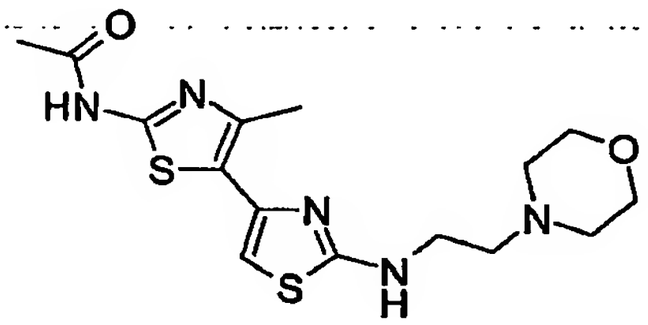


(30)

According to the general procedure 1, N-(3-hydroxyphenyl)thiourea (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 2 h. TEA (3 eq) is then added. After addition of water, the desired product is filtrated off and washed with water. Compound **(30)** is isolated as a kaki solid (79%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.12 (s, 3H), 2.47 (s, 3H), 6.38 (m, 1H), 6.86 (s, 1H), 7.01-7.09 (m, 3H), 9.36 (s, 1H), 10.15 (s, 1H), 11.85 (s, 1H). M^-(ESI): 345; M^+(ESI): 347. HPLC, Rt: 2.9 min (purity: 99.6 %).

Example 31: N-{4-methyl-2-[(2-morpholin-4-ylethyl)amino]-4,5-bi-1,3-thiazol-2-yl} acetamide, hydrochloride salt

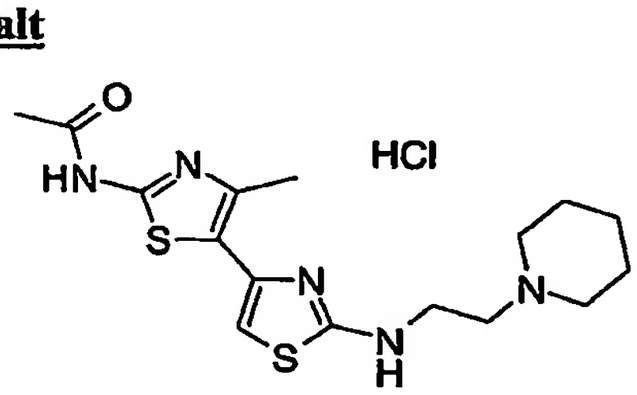


(31)

According to the general procedure 1, N-(2-morpholin-4-ylethyl)thiourea (Transwld) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydro bromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at r.t. for 4 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. It is then precipitated as HCl salt. Compound **(31)** is isolated as a pastel pink solid (42%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.14 (s, 3H), 2.45 (s, 3H), 3.18 (m, 2H), 3.39 (m, 3H), 3.73 (m, 3H), 3.81 (m, 2H), 3.98 (m, 2H), 6.74 (s, 1H), 8.04 (br s, 1H), 10.56 (br s, 1H), 12.04 (s, 1H). M^-(ESI): 366; M^+(ESI): 368. HPLC, Rt: 1.6 min (purity: 96.8 %).

Example 32: N-{4-methyl-2-[(2-piperidin-1-ylethyl)amino]-4,5-bi-1,3-thiazol-2-yl} acetamide, hydrochloride salt



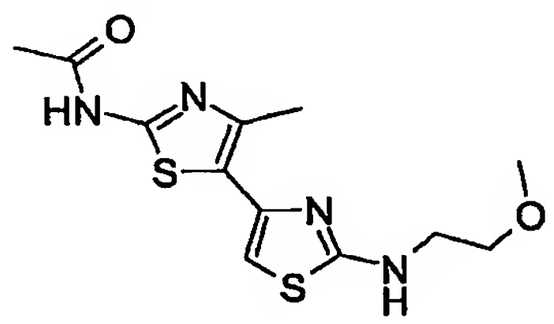
(32)

According to the general procedure 1, N-(2-piperidin-1-ylethyl)thiourea (Transwld) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide,

hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at r.t. for 4 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. It is then precipitate as HCl salt. Compound **(32)** is isolated as a mauve solid (74%).

^1H NMR (DMSO-d_6, 300 MHz) δ 1.33 (m, 1H), 1.62-1.87 (m, 5H), 2.08 (s, 3H), 2.39 (s, J=S Hz, 3H), 2.92 (m, 2H), 3.23 (m, 2H), 3.49 (m, 2H), 3.6-3.8 (m, 2H), 6.68 (s, 1H), 7.98 (br s, 1H), 9.74 (br s, 1H), 11.98 (s, 1H). M^-(ESI): 364; M^+(ESI): 366. HPLC, Rt: 1.8 min (purity: 97.4 %).

Example 33: N-{2-[(2-methoxyethyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl} acetamide

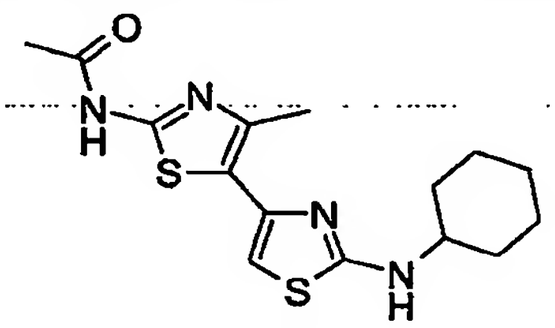


(33)

According to the general procedure 1, N-(2-methoxyethyl)thiourea (Transwld) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)**and TEA (3 eq) in EtOH. The mixture is stirred at r.t. for 4 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. Compound **(33)** is isolated as a dark green oil (quantitative).

^1H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 2.50 (s, 3H), 3.37 (s, 3H), 3.52 (m, 2H), 3.60 (m, 2H), 5.82 (br s, 1H), 6.40 (s, 1H), 10.97 (br s, 1H). M^-(ESI): 311; M^+(ESI): 313. HPLC, Rt: 1.6 min (purity: 97.7 %).

Example 34: N-[2-(cyclohexylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide

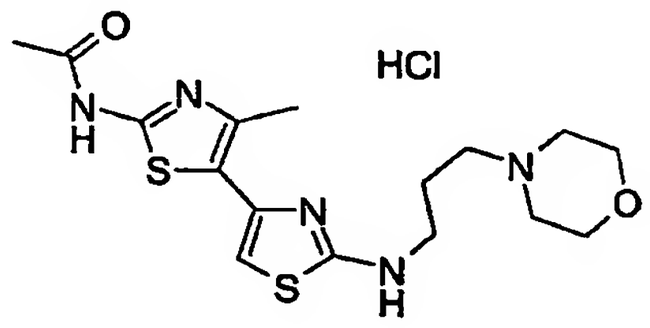


(34)

According to the general procedure 1, N-cyclohexylthiourea (Transwld) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at r.t. for 4 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. Compound **(34)** is isolated as a green foam (89%).

^1H NMR ($CDCl_3$, 300 MHz) δ 1.16-1.44 (m, 5H), 1.55-1.83 (m, 3H), 2.07 (m, 2H), 2.13 (s, 3H), 2.49 (s, 3H), 3.30 (m, 1H), 5.52 (d, J=9 Hz, 1H), 6.39 (s, 1H), 10.98 (br s, 1H). M^- (ESI): 335; M^+(ESI): 337. HPLC, Rt: 2.5 min (purity: 93 %).

Example 35: N-{4-methyl-2-[(3-morpholin-4-ylpropyl)amino]-4,5-bi-1,3-thiazol-2-yl} acetamide, hydrochloride salt



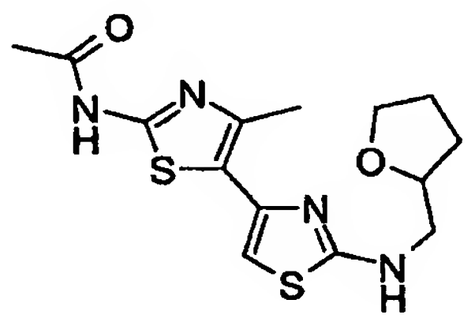
(35)

According to the general procedure 1, N-(3-morpholin-4-ylpropyl)thiourea (Transwld) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at r.t.

for 4 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. It is then precipitated as HCl salt. Compound **(35)** is isolated as a purple solid (82%).

^1H NMR (DMSO-d_6, 300 MHz) δ 2.05 (m, 2H), 2.14 (s, 3H), 2.44 (s, 3H), 2.98-3.26 (m, 4H), 3.31-3.54 (m, 4H), 3.79 (m, 2H), 3.98 (m, 2H), 6.69 (s, 1H), 8.00 (br s, 1H), 10.70 (br s, 1H), 12.04 (s, 1H). M^-(ESI): 380; M^+(ESI): 382. HPLC, Rt: 1.3 min (purity: 98.5 %).

Example 36: N-{4-methyl-2-[(tetrahydrofuran-2-ylmethyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide

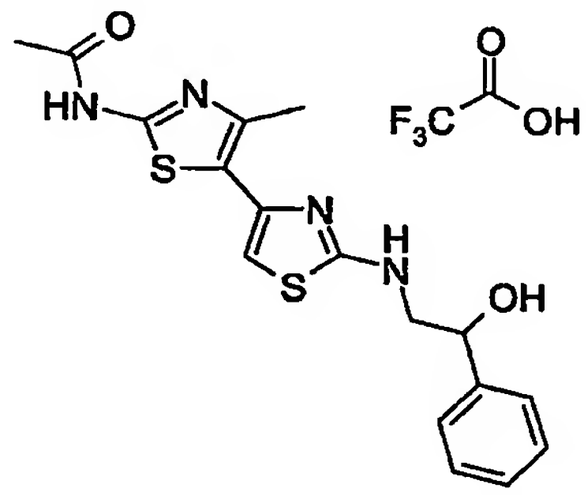


(36)

According to the general procedure 1, N-(tetrahydrofuran-2-ylmethyl)thiourea (Transwld) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at r.t. for 4 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. Compound **(36)** is isolated as a light green solid (quantitative).

^1H NMR ($CDCl_3$, 300 MHz) δ 1.59-1.70 (m, 1H), 1.86-2.07 (m, 3H), 2.15 (s, 3H), 2.24 (s, 3H), 3.28 (m, 1H), 3.56 (m, 1H), 3.76 (m, 1H), 3.87 (m, 1H), 4.14 (m, 1H), 5.96 (br s, 1H), 6.38 (s, 1H), 11.01 (br s, 1H). M^-(ESI): 337.3; M^+(ESI): 339.3. HPLC, Rt: 1.8 min (purity: 94.4 %).

Example 37: N-{2-[(2-hydroxy-2-phenylethyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl} acetamide, trifluoroacetate salt

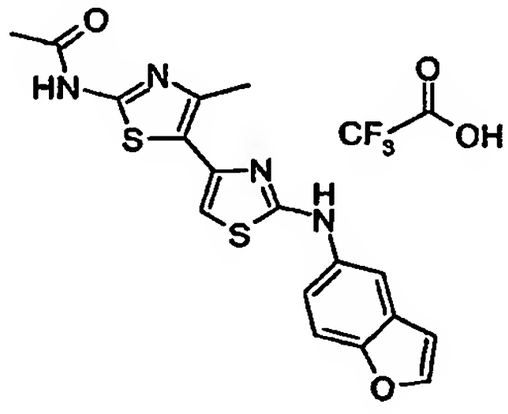


(37)

According to the general procedure 1, N-(2-hydroxy-2-phenylethyl)thiourea (obtained from 2-amino-1-phenylethanol from Fluka following procedure C) is added to a solution of of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture is stirred at reflux for 2 h. TEA (3 eq) is then added. The solvents are evaporated and the desired product is purified by preparative HPLC. Compound **(37)** is isolated as a yellow solid (32%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.14 (s, 3H), 2.45 (s, 3H), 3.31 (d, J=9 Hz, 1H), 3.51 (d, J=6 Hz, 1H), 4.48 (br s, 1H), 4.88 (d, J=6 Hz, 1H), 6.64 (s, 1H), 7.22-7.47 (m, 6H), 7.98 (br s, 1H), 12.01 (s, 1H). M^-(ESI): 373; M^+(ESI): 375. HPLC, Rt: 2.3 min (purity: 97.2 %).

Example 38: N-[2-(1-benzofuran-5-ylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl] acetamide, trifluoroacetate salt

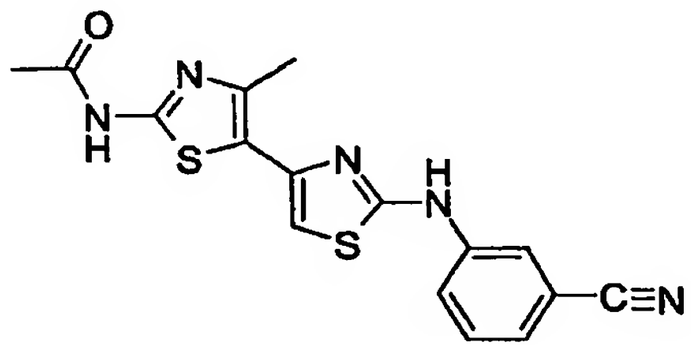


(38)

According to the general procedure 1, N-1-benzofuran-5-ylthiourea (Bionet) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide, hydrobromide salt **(Intermediate 1)** and TEA (3 eq) in EtOH. The mixture was stirred at r.t. for 1 h. TEA (3 eq) is then added. The solvents are evaporated and the desired product is purified by preparative HPLC. Compound **(38)** is isolated as a light rose solid (36%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.13 (s, 3H), 2.49 (s, 3H), 6.84 (s, 1H), 6.89 (m, 1H), 7.45 (m, 1H), 7.55 (m, 1H), 7.95 (m, 1H), 8.01 (m, 1H), 10.26 (s, 1H), 12.04 (br s, 1H). M^- (ESI): 369; M^+(ESI): 371. HPLC, Rt: 3.5 min (purity: 99.8 %).

Example 39: N-{2-[(3-cyanophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide

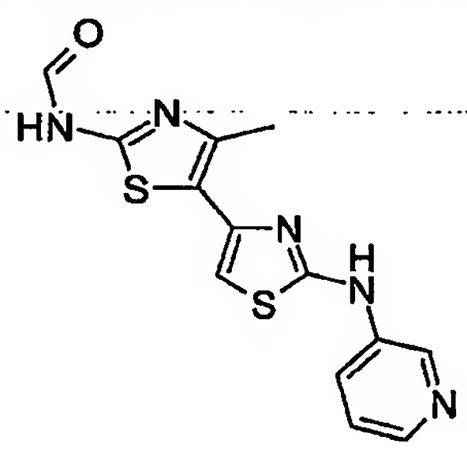


(39)

According to the general procedure 1, 1-(3-cyanophenyl)-2-thiourea (Transwld) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-thiazol-2-yl]acetamide **(Intermediate 1)** in EtOH. The mixture is stirred at r.t. for 17 h. TEA (3 eq) is then added. The solvents are evaporated and the desired product is purified by flash chromatography. Compound **(39)** is isolated as light yellow solid (43%).

^{1}H NMR (DMSO-d_6) δ: 2.13 (s, 3H), 2.49 (s, 3H), 6.99 (s, 1H), 7.40 (m, 1H), 7.53 (m, 1H), 7.80 (m, 1H), 8.24 (m, 1H), 10.70 (s, 1H), 12.07 (s, 1H). M^-(ESI): 356; M^+(ESI): 354. HPLC, Rt: 3.5 min (purity: 95.79%).

Example 40: [4-methyl-2-(pyridin-3-ylamino)-4,5-bi-1,3-thiazol-2-yl]formamide



(40)

Step I: 4-methyl-N-2-pyridin-3-yl-4,5-bi-1,3-thiazole-2,2-diamine

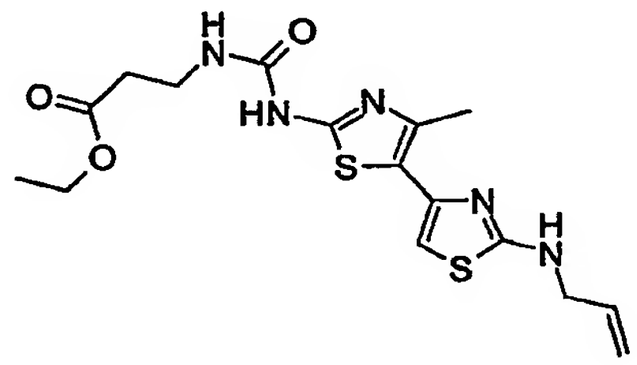
According to the general procedure 1, 3-pyridylthiourea (Lancaster) is added to a solution of 1-(2-amino-4-methyl-1,3-thiazol-5-yl)-2-bromoethanone, hydrobromide salt **(Intermediate 2)** and TEA (3 eq) in EtOH. The mixture is stirred at r.t. for 2 hours. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. It is then purified by flash chromatography. 4-methyl-N-2-pyridin-3-yl-4,5-bi-1,3-thiazole-2,2-diamine is isolated as light yellow solid in 95% yield. M^-(ESI): 288.2; M^+(ESI): 290.1. HPLC, Rt: 1.2 min (purity: 99.6%).

Step II: [4-methyl-2-(pyridin-3-ylamino)-4,5-bi-1,3-thiazol-2-yl]formamide **(40)**

In a microwave tube, 4-methyl-N-2-pyridin-3-yl-4,5-bi-1,3-thiazole-2,2-diamine obtained in Step I as described above (58.0 mg; 0.20 mmol; 1.00 eq.) is dissolved in formic acid (2.00 ml). The mixture is heated twice to 130°C for 30 min in the microwave. A conversion of 50% is afforded. Solvents are evaporated and the desired product is isolated by preparative HPLC. Compound **(40)** is isolated as dark yellow solid (13 mg, 21% yield).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.53 (s, 3H), 7.06 (s, 1H), 7.55 (m, 1H), 8.20 (m, 1H), 8.27 (m, 1H), 8.48 (s, 1H), 9.01 (s, 1H), 10.77 (s, 1H), 12.00 (s, 1H). M^-(ESI): 316.3; M^+(ESI): 318.3. HPLC, Rt: 1.9 min (purity: 97.4 %).

Example 41: ethyl N-({[2-(allylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino} carbonyl)-beta-alaninate



(41)

Step I: N-2-allyl-4-methyl-4,5-bi-1,3-thiazole-2,2-diamine

According to the general procedure 1, N-allylthiourea (Fluka) is added to a solution of 1-(2-amino-4-methyl-1,3-thiazol-5-yl)-2-bromoethanone, hydrobromide salt **(Intermediate 2)** and TEA (3 eq) in EtOH. The mixture is stirred at r.t. for 1 h. TEA (3 eq) is then added. After addition of water, the desired product is extracted with EtOAc (3 fractions) and dried over $MgSO_4$. It is then purified by flash chromatography. N-2-allyl-4-methyl-4,5-bi-1,3-thiazole-2,2-diamine is isolated as colorless solid (175 mg, 70% yield).

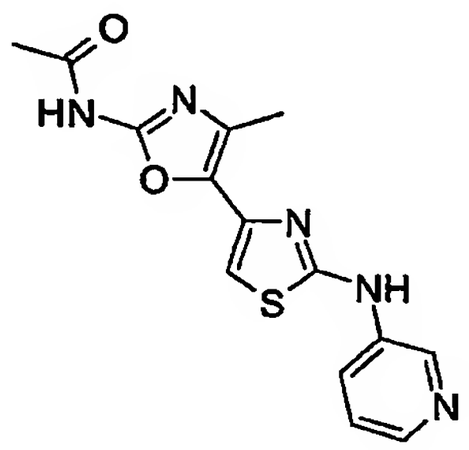
M^+(ESI): 253.1. HPLC, Rt: 1.5 min (purity: 92.0%).

Step II: ethyl N-({[2-(allylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}carbonyl)-beta-alaninate **(41)**

To a solution of N-2-allyl-4-methyl-4,5-bi-1,3-thiazole-2,2-diamine obtained in Step I as described above (60.60 mg; 0.18 mmol; 1.00 eq.) in DCM (2.00 ml) is added to commercial N-ethyldiisopropylamine (0.07 ml; 0.40 mmol; 2.20 eq.) and commercial ethyl 3-isocyanatopropionate (26.03 mg; 0.18 mmol; 1.00 eq.). The mixture is stirred under reflux for 5 hours, and the solvents are evaporated. The resulting product is purified by preparative HPLC. The purified fraction is diluted with EtOAc and washed with $NaHCO_3$, affording compound **(41)** as dark oil (28.2 mg; 39%).

^{1}H NMR (DMSO-d_6) δ: 1.18 (m, 3H), 2.35 (s, 3H), 2.50 (m, 2H), 3.36 (m, 2H), 3.86 (m, 2H), 4.04 (m, 2H), 5.11 (m, 1H), 5.24 (m, 1H), 5.90 (m, 1H), 6.52 (s, 1H), 6.68 (m, 1H), 7.83 (m, 1H), 10.29 (br s, 1H). M^-(ESI): 394; M^+(ESI): 396. HPLC, Rt: 2.5 min (purity: 98.36%).

Example 42: N-{4-methyl-5-[2-(pyridin-3-ylamino)-1,3-thiazol-4-yl]-1,3-oxazol-2-yl} acetamide, trifluoroacetate salt



(42)

According to the the general procedure 1, 3-pyridylthiourea (Lancaster) is added to a solution of N-[5-(bromoacetyl)-4-methyl-1,3-oxazol-2-yl]acetamide **(Intermediate 3)** in EtOH. The mixture is stirred 17 h at –20°C, then 5 h at r.t. The desired product is filtrated off the reaction mixture. It is further purified by preparative HPLC. Compound **(42)** is isolated as a yellow solid (5%).

^{1}H NMR (Methanol-d_4) δ: 2.21 (s, 3H), 2.52 (s, 3H), 7.07 (s, 1H), 7.93 (m, 1H), 8.43 (m, 3H), 9.55 (s, 1H). M^-(ESI): 314; M^+(ESI): 316. HPLC, Rt: 1.5 min (purity: 96.03%).

The following compounds can be synthesized according to the general schemes proposed herein and are commercially available:

N-{2-[(4-ethoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(4-methylphenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(4-{[(4,6-dimethylpyrimidin-2-yl)amino]sulfonyl}phenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-[2-(allylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]propanamide;

N-{2-[(4-{[(2,6-dimethoxypyrimidin-4-yl)amino]sulfonyl}phenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)amino]-4,5-bi-1,3-thiazol-2-yl}propanamide;

N-{2-[(4-{[(4,6-dimethylpyrimidin-2-yl)amino]sulfonyl}phenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}propanamide;

N-(4-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}phenyl)acetamide;

N-{4-methyl-2-[(3-nitrophenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(4-aminophenyl)amino]-4-methyl-4,5'-bi-1,3-thiazol-2-yl}acetamide;

3-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}benzoic acid;

N-{2-[(2-ethylphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(2-methylphenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(4-bromophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-(2-{[4-(aminosulfonyl)phenyl]amino}-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide;

N-{2-[(2,5-dimethoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(3-acetylphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-(2-{[4-(dimethylamino)phenyl]amino}-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide.

Example 43 : Biological assays

The compounds of the present invention may be subjected to the following assays:

a) **High Throughput PI3K lipid kinase assay (binding assay):**

The efficacy of compounds of the invention in inhibiting the PI3K induced-lipid phosphorylation may be tested in the following binding assay.

The assay combines the scintillation proximity assay technology (SPA; Amersham) with the capacity of neomycin (a polycationic antibiotic) to bind phospholipids with high affinity and specificity. The Scintillation Proximity Assay is based on the properties of weakly emitting isotopes (such as ^{3}H, ^{125}I, ^{33}P). Coating SPA beads with neomycin allows the detection of phosphorylated lipid substrates after incubation with recombinant PI3K and radioactive ATP in the same well, by capturing the radioactive phospholipids to the SPA beads through their specific binding to neomycin.

To a 384 wells MTP containing 5 µl of the test compound of Formula (I) (solubilized in 6% DMSO; to yield a concentration of 100, 30, 10, 3, 1,0.3, 0.1, 0.03, 0.01, 0.001 µM of the test compound), the following assay components are added. **1)** 5 µl (58 ng) of Human recombinant GST-PI3Kγ (in Hepes 40 mM, pH 7.4, DTT 1 mM and ethylenglycol 5%) **2)** 10 µl of lipid micelles and **3)** 10 µl of Kinase buffer ([^{33}P]γ–ATP 45µM/60nCi, $MgCl_2$ 30mM, DTT 1mM, β–Glycerophosphate 1mM, Na_3VO_4 100 µM, Na Cholate 0.3 %, in Hepes 40 mM, pH 7.4). After incubation at room temperature for 180 minutes, with gentle agitation, the reaction is stopped by addition of 60 µl of a solution containing 100 µg of neomycin-coated PVT SPA beads in PBS containing ATP 10mM and EDTA 5mM. The assay is further incubated at room temperature for 60 minutes with gentle agitation to allow binding of phospholipids to neomycin-SPA beads. After precipitation of the neomycin-coated PVT SPA beads for 5 minutes at 1500 x g, radioactive PtdIns(3)P is quantified by scintillation counting in a Wallac MicroBeta ™ plate counter.

The values indicated in Table I below refer to the IC_{50} (nM) with respect to PI3Kγ, i.e. the amount necessary to achieve 50% inhibition of said target. Said values show a considerable inhibitory potency of thiazole compounds with regard to PI3Kγ.

Examples of inhibitory activities for compounds of of the invention are set out in Table I below.

Table I: IC_{50} values of thiazole derivatives against PI3Kγ.

Example No	*PI3Kγ IC50 (nM)*
1	10
5	630
6	202
7	94
14	575
16	844
22	314
31	871
34	211
37	70

b) Cell based ELISA to monitor PI3K inhibition:

The efficacy of compounds of the invention in inhibiting the PI3K induced Akt/PKB phosphorylation may be tested in the following cell based assay.

Measurement of Akt/PKB phosphorylation in macrophages after stimulation with Complement 5a: Raw 264: Raw 264-7 macrophages (cultured in DMEM-F12 medium containing 10% Fetal Calf serum and antibiotics) are plated at 20'000 cells/well in a 96 MTP 24 h before cell stimulation. Previous to the stimulation with 50 nM of Complement 5a during 5 minutes, Cells are serum starved for 2h, and pretreated with inhibitors for 20 minutes. After stimulation cells are fixed in 4% formaldehyde for 20 minutes and washed 3 times in PBS containing 1% Triton X-100 (PBS/Triton). Endogenous peroxidase is blocked by a 20 minutes incubation in 0.6% H_2O_2 and 0.1% Sodium Azide in PBS/Triton and washed 3 times in PBS/Triton. Cells are then blocked by 60 minutes incubation with 10%

fetal calf serum in PBS/Triton. Next, phosphorylated Akt/PKB is detected by an overnight incubation at 4°C with first antibody (anti phospho Serine 473 Akt IHC, Cell Signaling) diluted 800-fold in PBS/Triton, containing 5% bovine serum albumin (BSA). After 3 washes in PBS/Triton, cells are incubated for 60 minutes with a peroxidase conjugated goat-anti-rabbit antibody (1/400 dilution in PBS/Triton, containing 5% BSA), washed 3 times in PBS/Triton, and 2 times in PBS and further incubated in 100 µl of substrate reagent solution (R&D) for 20 minutes. The reaction is stopped by addition of 50 µl of 1 M SO_4H_2 and absorbance is read at 450 nm.

The values indicated in Table II below reflect the percentage of inhibition of AKT phoshorylation as compared to basal level. Said values show a clear effect of the thiazole compounds on the activation of AKT phosphorylation in macrophages.

Examples of inhibitory activities for compounds of the invention are set out in Table II below.

Table II: IC_{50} values of thiazole derivatives in Cell Assay

Example No	*Cell Assay (P-Akt, Elisa) IC50 [µM]*
1	3.18
7	1.64
24	0.66

Example 44 : Preparation of a pharmaceutical formulation

The following formulation examples illustrate representative pharmaceutical compositions according to the present invention being not restricted thereto.

Formulation 1 – Tablets

A compound of Formula (I) is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ration. A minor amount of magnesium stearate is added as a

lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg) of active thiazole compound per tablet) in a tablet press.

Formulation 2 – Capsules

A compound of Formula (I) is admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active thiazole compound per capsule).

Formulation 3 – Liquid

A compound of Formula (I) (1250 mg), sucrose (1.75 g) and xanthan gum (4 mg) are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously prepared solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added to produce a total volume of 5 mL.

Formulation 4 – Tablets

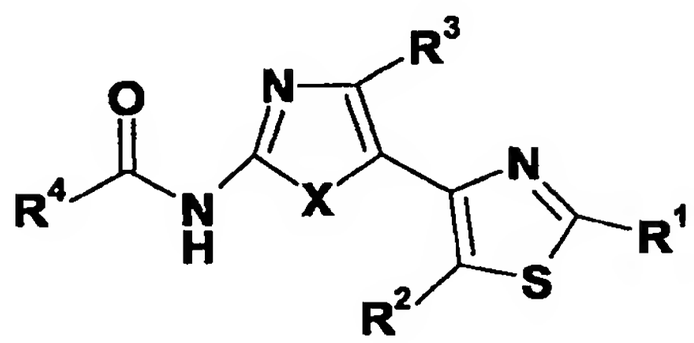
A compound of Formula (I) is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active thiazole compound) in a tablet press.

Formulation 5 – Injection

A compound of Formula (I) is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/ml.

Claims

1. A thiazole derivative according to Formula (I),



(I)

wherein R^1 is a moiety of the formula $-NR^5R^6$;

R^2, R^3 and R^5 are selected independently from H, C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkynyl;

R^4 is selected from H, C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkynyl and NR^8R^9 wherein R^8 and R^9 are independently selected from H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl and C_1-C_6-alkyl acyloxy;

R^6 is selected from C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkyl alkoxy, aryl, heteroaryl, C_3-C_8-cycloalkyl, C_3-C_8-heterocycloalkyl, aryl C_1-C_6-alkyl, heteroaryl C_1-C_6-alkyl, C_3-C_8-cycloalkyl C_1-C_6-alkyl and C_3-C_8-heterocycloalkyl C_1-C_6-alkyl; or $R^5$and R^6, together with the carbon atoms they are linked to, form a 5-8-membered saturated, partially unsaturated or aromatic ring containing optionally one or more heteroatoms selected from O, N and S;

X is selected from S and O; as well as isomers, of these for use as a medicament.

2. A thiazole derivative according to claim 1 wherein R^2 is H.

3. A thiazole derivative according to claims 1 to 2 wherein R^3 is methyl.

4. A thiazole derivative according to any one of the preceding claims wherein R^4 is selected from C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkynyl.

5. A thiazole derivative according to any one of the preceding claims wherein R^5 is H and R^6 is selected from C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkyl alkoxy and C_3-C_8-cycloalkyl C_1-C_6-alkyl and C_3-C_8-heterocycloalkyl C_1-C_6-alkyl.

6. A thiazole derivative according to any one of the claims 1 through 4 wherein R^5 is H and R^6 is selected from aryl C_1-C_6-alkyl and heteroaryl C_1-C_6-alkyl,

7. A thiazole derivative according to any one of the claims 1 through 4 wherein R^5 is H and R^6 is selected from aryl and heteroaryl.

8. A thiazole derivative according according to any one of the claims 1 through 4 wherein R^5 and R^6, together with the carbon atoms they are linked to, form a 5-8-membered saturated, partially unsaturated or aromatic ring containing optionally one or more heteroatoms selected from O, N and S.

9. A thiazole derivative according according to claim 8 wherein R^5 and R^6, together with the carbon atoms they are linked to, form a 5-8-membered saturated ring optionally additionally containing an oxygen atom.

10. A thiazole derivative according to any one of the preceding claims, selected from the following group:

3-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}benzoic acid;

4-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}benzoic acid;

N-[2-(benzylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide;

N-{4-methyl-2-[(2-phenylethyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-(4-methyl-2-piperidin-1-yl-4,5-bi-1,3-thiazol-2-yl)acetamide;

N-[2-(allylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide;

N-[4-methyl-2-(pyridin-3-ylamino)-4,5-bi-1,3-thiazol-2-yl]acetamide;

N-[4-methyl-2-(pyridin-2-ylamino)-4,5-bi-1,3-thiazol-2-yl]acetamide;

N-{2-[(4-methoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(4-hydroxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(4-nitrophenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

4-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}benzamide;

N-[2-({4-[(4-benzylpiperazin-1-yl)carbonyl]phenyl}amino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide;

N-(2-amino-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide;

N-(2-anilino-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide;

N-(4-methyl-2-morpholin-4-yl-4,5-bi-1,3-thiazol-2-yl)acetamide;

N-[4-methyl-2-(4-methylpiperazin-1-yl)-4,5-bi-1,3-thiazol-2-yl]acetamide;

Methyl 1-[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]piperidine-3-carboxylate;

N-{2-[4-(2-hydroxyethyl)piperidin-1-yl]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-(4-methyl-2-pyrrolidin-1-yl-4,5-bi-1,3-thiazol-2-yl)acetamide;

N-[2-(3-hydroxypyrrolidin-1-yl)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide;

N-[2-(tert-butylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide;

N-{2-[(6-methoxypyridin-3-yl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(6-chloropyridin-3-yl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(4-cyanophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(4-chlorophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(2-chlorophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(2-methoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(3-chlorophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(3-hydroxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(2-morpholin-4-ylethyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(2-piperidin-1-ylethyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(2-methoxyethyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-[2-(cyclohexylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide;

N-{4-methyl-2-[(3-morpholin-4-ylpropyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(tetrahydrofuran-2-ylmethyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(2-hydroxy-2-phenylethyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-[2-(1-benzofuran-5-ylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]acetamide;

N-{2-[(3-cyanophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

[4-methyl-2-(pyridin-3-ylamino)-4,5-bi-1,3-thiazol-2-yl]formamide;

Ethyl N-({[2-(allylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}carbonyl)-beta-alaninate;

N-{4-methyl-5-[2-(pyridin-3-ylamino)-1,3-thiazol-4-yl]-1,3-oxazol-2-yl}acetamide;

N-{2-[(4-ethoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(4-methylphenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(4-{[(4,6-dimethylpyrimidin-2-yl)amino]sulfonyl}phenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-[2-(allylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]propanamide;

N-{2-[(4-{[(2,6-dimethoxypyrimidin-4-yl)amino]sulfonyl}phenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)amino]-4,5-bi-1,3-thiazol-2-yl}propanamide;

N-{2-[(4-{[(4,6-dimethylpyrimidin-2-yl)amino]sulfonyl}phenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}propanamide;

N-(4-{[2-(acetylamino)-4-methyl-4,5-bi-1,3-thiazol-2-yl]amino}phenyl)acetamide;

N-{4-methyl-2-[(3-nitrophenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(4-aminophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(2-ethylphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{4-methyl-2-[(2-methylphenyl)amino]-4,5-bi-1,3-thiazol-2-yl}acetamide;

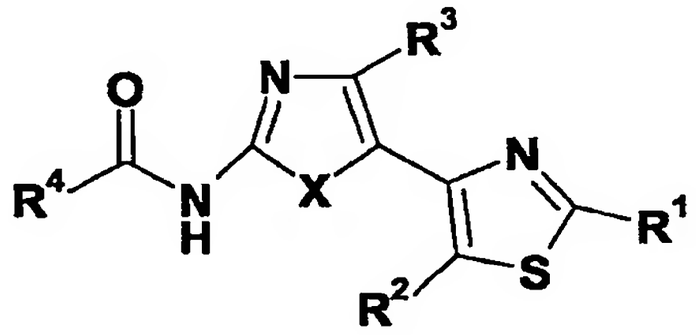
N-{2-[(4-bromophenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-(2-{[4-(aminosulfonyl)phenyl]amino}-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide;

N-{2-[(2,5-dimethoxyphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide;

N-{2-[(3-acetylphenyl)amino]-4-methyl-4,5-bi-1,3-thiazol-2-yl}acetamide; N-(2-{[4-(dimethylamino)phenyl]amino}-4-methyl-4,5-bi-1,3-thiazol-2-yl)acetamide.

11. Use of a thiazole derivative according to Formula (I):



(I)

wherein R^1 is a moiety of the formula $-NR^5R^6$;

R^2, R^3 and R^5 are selected independently from H, C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkynyl;

R^4 is selected from H or C_1-C_6-alkyl, C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkynyl and NR^8R^9 wherein R^8 and R^9 are independently selected from C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkynyl;

R^6 is selected from H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkyl alkoxy, aryl, heteroaryl, C_3-C_8-cycloalkyl, C_3-C_8-heterocycloalkyl, aryl C_1-C_6-alkyl, heteroaryl C_1-C_6-alkyl, C_3-C_8-cycloalkyl C_1-C_6-alkyl and C_3-C_8-heterocycloalkyl C_1-C_6-alkyl; or $R^5$and R^6, together with the carbon atoms they are linked to, form a 5-8-membered saturated, partially unsaturated or aromatic ring containing optionally one or more heteroatoms selected from O, N and S; X is selected from O and S; as well as isomers and mixtures of these for the preparation of a medicament for the prophylaxis and/or treatment of autoimmune disorders and/or inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, kidney diseases, platelet aggregation, cancer, transplantation, graft rejection or lung injuries.

12. Use according to claim 11, wherein said diseases are selected in the group including multiple sclerosis, psoriasis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosis, inflammatory bowel disease, lung inflammation, thrombosis or brain infection/inflammation such as meningitis or encephalitis.

13. Use according to claim 11, wherein said diseases are selected in the group including Alzheimer's disease, Huntington's disease, CNS trauma, stroke or ischemic conditions.

14. Use according to claim 11, wherein said diseases are selected in the group including atherosclerosis, heart hypertrophy, cardiac myocyte dysfunction, elevated blood pressure or vasoconstriction.

15. Use according to claim 11, wherein said diseases are selected in the group including chronic obstructive pulmonary disease, anaphylactic shock fibrosis, psoriasis, allergic diseases, asthma, stroke or ischemic conditions, ischemia-reperfusion, platelets aggregation/activation, skeletal muscle atrophy/hypertrophy, leukocyte recruitment in cancer tissue, angiogenesis, invasion metastisis, in particular melanoma, Karposi's sarcoma, acute and chronic bacterial and viral infections, sepsis, graft rejection, glomerulo sclerosis, glomerulo nephritis, progressive renal fibrosis, endothelial and epithelial injuries in the lung or in general lung airways inflammation.

16. Use according to any of claims 11 to 15 for the modulation, in particular for the inhibition, of the PI3 kinase activity.

17. Use according to claim 16, wherein said PI3 kinase is a PI3 kinase γ.

18. A pharmaceutical composition containing at least one thiazole derivative according to any of claims 1 to 10 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

Abstract of the invention:

The present invention is related to thiazole derivatives of Formula (I) in particular for the treatment and/or prophylaxis of autoimmune disorders and/or inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, kidney diseases, platelet aggregation, cancer, transplantation, graft rejection or lung injuries.